Acta Genetica et Statistica Medica

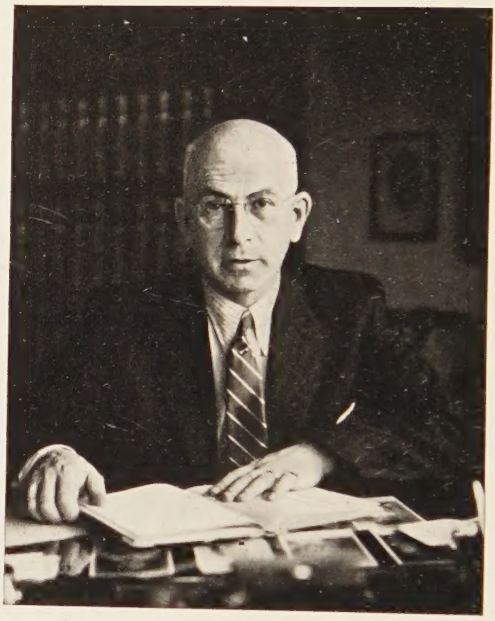
Vol. 9, No. 2 1959

BASEL (Schweiz) S. KARGER NEW YORK

Printed in Switzerland

INDEX

Dr. Dr. h. c. Heinz Karger †



Heinz Karger

Dr. Dr. h. c. Heinz Karger

Der Verleger der «Acta Genetica et Statistica Medica», Dr. Dr. h. c. H. Karger, ist am 27. März unerwartet einem Herzinfarkt erlegen.

Der Gründer der «Acta Genetica», weiland Professor Gunnar Dahlberg, hat mir, wie in vielen anderen wichtigen Angelegenheiten, tatkräftig geholfen, als Dr. Karger und ich begannen, die «International Archives of Allergy and Applied Immunology» herauszugeben. Gunnar Dahlberg bot sich hierbei Gelegenheit, die unermüdliche Tatkraft, weise Voraussicht und Generosität von Heinz Karger kennenzulernen. Er hat auch mit Freude und Bewunderung verfolgt, wie die Freundschaft und das gegenseitige Vertrauen zwischen Heinz Karger und mir die eigentliche Grundlage dafür gebildet haben, daß Heinz Karger trotz Schwierigkeiten und anfänglich schlechten ökonomischen Aussichten ohne Zögern die Herausgabe der «Archives» weiter gefördert und schließlich zum Erfolg geführt hat. Daher war es selbstverständlich, daß Gunnar Dahlberg, als er die Gründung einer Zeitschrift für sein Spezialfach plante, mich anfragte, ob ich glaube, daß Heinz Karger die Herausgabe übernehmen würde. In dieser Weise war es mir vergönnt, Heinz Karger und Gunnar Dahlberg in persönlichen Kontakt zu bringen. Aus diesem Kontakt ist nicht nur eine förderliche Zusammenarbeit, sondern auch eine treue Freundschaft entstanden. In vertrauensvoller Zusammenarbeit wurde dann die «Acta Genetica et Statistica Medica» zu dem bedeutungsvollen Organ entwickelt, das sie heute darstellt. Es hat nicht an Schwierigkeiten gefehlt, aber die hingebungsvolle Arbeit des Editors und Verlegers hat sie auch in diesem Falle überwunden. Heinz Karger hat mit verständnisvoller Bewunderung wesentlich dazu beigetragen, daß Gunnar Dahlberg trotz seiner schweren körperlichen Behinderung die Zeitschrift so erfolgreich weiterentwickeln konnte. Ich kann bezeugen, was dies für Gunnar Dahlberg in den schweren Jahren seiner Krankheit bedeutet hat. Ich bin davon überzeugt, daß die «Acta Genetica et Statistica Medica» die Erinnerung dieser beiden Persönlichkeiten und die Bedeutung ihres gemeinsamen Werkes lebendig erhalten wird.

Paul Kallós, Helsingborg

VanArsdel, P. P., Jr. and Motulsky, A. G.: Acta genet. *9* : 101—114 (1959)

From the Department of Medicine, University of Washington School of Medicine, Seattle, Wash.

FREQUENCY AND HEREDITABILITY OF ASTHMA AND ALLERGIC RHINITIS IN COLLEGE STUDENTS[1]

By PAUL P. VAN ARSDEL Jr. and ARNO G. MOTULSKY

With the technical assistance of *Gabrielle Bouchard* and *Sue Stevens*

Observations on the familial occurrence of allergy, particularly asthma, extend back at least 300 years *(Wiener, Zieve and Fries*, 1936). Early in this century studies were still handicapped because little lay knowledge existed concerning the nature of asthma and "hayfever". Family histories were thus quite unreliable except when all members were interviewed and examined personally. Striking pedigrees demonstrating the high incidence of asthma and other allergies in a few selected families were often obtained and used as evidence for the genetic transmission of these disorders. Attempts to relate these observations to Mendelian laws have been unsatisfactory since it is now generally recognized that pedigrees from individual families are difficult to interpret in common disorders such as asthma and other allergic diseases *(Ratner and Silberman*, 1952).

Studies on the incidence of family allergy in a large group of allergic patients have provided more appropriate data for analysis, but rarely has an attempt been made to study family incidence simultaneously in a comparable non-allergic control group. Even in the most complete recent study on the heredity of bronchial asthma *(Schwartz*, 1952), the control group consisted of 200 non-allergic subjects seeking medical treatment for other unrelated disorders; this group was not strictly comparable to the allergic population. There is thus considerable need for further studies concerning the incidence of allergy and family history of allergy in un-

[1] Supported by a grant from the Smith Kline and French Foundation and grant number H-3091 from the National Institutes of Health.

selected members of a large group. Our objective, therefore, was to evaluate *all* individuals in a relatively homogeneous population of college students of sufficient size so that some conclusions could be reached concerning allergic disease among its members and their families. The opportunity for such a study was provided by data which was originally obtained for comparing the blood group distribution and secretor status of the allergic and non-allergic members of this population.

Method of Study

Since each newly registered student at the University of Washington in Seattle obtained a medical examination at the University Health Center, a convenient method for obtaining historical and confirmatory information concerning asthma and allergic rhinitis ("hayfever") was available. All students were asked to fill out the questionnaire which is reproduced in Fig. 1. The information concerning seasonal occurrence and years when symptoms occurred was helpful in evaluating the validity of the responses.

All students who registered for the first time between December 1956 and October 1957 were evaluated. A majority of these students was from 18 to 20 years of age, and over 80% were under 25 years of age. The group analysed consisted of 4,110 men and 1,708 women, a total of 5,818 individuals. Blood group and secretor status data on this population will be published elsewhere.

Results

A. Occurrence of Disease in the Population

A classification of all individuals according to the nature of their allergic history is shown in Table I. Although asthma and "hayfever" were the only allergic disorders considered, it is significant that these were reported by over 16% of the population: 12% had "hayfever" only, 2.7% had both "hayfever" and asthma, and 2% reported asthma alone.

Over three-fourths of all persons with a "hayfever" history reported significant seasonal variations (all symptoms limited to the winter were considered "non-seasonal"). Only about one-third of those with a history of asthma alone had a similar seasonal variation (Table II).

B. Family History

In Table III A, the presence or absence of allergy in any family member (see Fig. 1) is correlated with the personal allergy history. A high proportion (56.5%) of allergic individuals reported allergic disease in their fa-

Fig. 1. Blood Group – Allergy Survey

Date

Last Name First Middle Age

Address Telephone

Have you *ever* had:

Asthma Yes ..... If yes, please indicate
No ..... years so afflicted: .....

Hayfever Yes ..... If yes, please indicate
No ..... years so afflicted: .....

Allergy in Family?

		Asthma	Hayfever
Mother's side	Mother		
	Grandparents		
	Aunts, Uncles		
	Cousins		
Father's side	Father		
	Grandparents		
	Aunts, Uncles		
	Cousins		
	Brothers, Sisters		
	Children		

Are you a Twin? ..... If yes, Identical ..... Unidentical .....

Does your twin have: Asthma ..... Hayfever .....

Seasons when *your* symptoms are or were worst:

	All seasons	Winter	Spring	Summer	Fall
Asthma					
Hayfever					

Have you been skin tested? ..... When? .....

By whom? ....
Name Address

Table I: Asthma and "Hayfever" in a Student Population

	Males		Females		Both	
	Number	% of Total	Number	% of Total	Number	% of Total
Total	4110	100	1708	100	5818	100
Allergic	649	15.8	322	18.9	971	16.7
Asthma only	90	2.2	28	1.6	118	2.0
"Hayfever" only	456	11.1	239	14.1	695	12.0
Both asthma and "hayfever"	103	2.5	55	3.2	158	2.7

Table II: Seasonal vs. Non-seasona lOccurrence of Symptoms

	Non-seasona	Seasonal	% Seasonal
Males	147	502	77.4%
Females	72	250	77.7
Asthma	76	42	35.6%
"Hayfever"	117	578	83.3
Asthma with "Hayfever"	26	132	83.5
Total	219	752	77.5%

milies, while 22.2% of those without personal allergy also claimed a positive family history. The reporting of allergy in the immediate family is likely to provide more information for dependable comparison, so that positive reports limited to parents and siblings were also tabulated. Again, a significant difference occurred, the allergic group reporting a 43.9% incidence and the non-allergic group, 16.1% (Table III B).[1]

The frequency of bilateral and unilateral family allergic histories is presented in Table III C, such information being correlated with the personal allergic history. A significant difference between allergic and non-allergic individuals occurred in the category with bilateral family involve-

[1] Positive family history reports from allergic females were significantly greater than those from allergic males (63.4% vs. 53.1%, $\chi^2 = 9.19$, $P = 0.0025$) perhaps indicating the greater awareness of more remote relatives by the girls. This interpretation was strengthened when parents and siblings were considered alone (Table III B): the difference between the male and female groups was then insignificant (47.2% vs. 42.2%, $p > 0.1$).

ment (11.5% vs. 6.4%); this difference was even more pronounced when related to those who had suffered from both asthma and "hayfever" (19.3%).

The incidence of allergy in parents alone was next determined, allergic students reporting 19.7%, the non-allergics 5.6% (Table IV A). For evaluating the heritability of disease, it was also necessary to establish the frequency of biparental and uniparental allergy, and this information is given in Table IV B. The students were divided into groups, Group A: those who reported asthma and/or "hayfever" in both parents, Group B: in only one parent, and Group C: in neither parent. Fifty-eight per cent of the students of Group A had had asthma or "hayfever", and significantly lower proportions were observed in Groups B and C (38.4% and 12.5% respectively). The large proportion of allergic students without parental allergy (63.5%) is also noteworthy.

Those allergic students who reported a history of both asthma and "hayfever" reported familial allergy considerably more frequently than did the other allergic groups (Tables III and IV).

Discussion

In spite of its known defects, the questionnaire used in this study provided valuable information which could not have been otherwise obtained from every member of an unselected large population. The seasonal incidence of symptoms gave support to our assumption of allergic origin for most of the positive reports of "hayfever", which could be easily confused with non-allergic conditions by laymen. Errors in reporting were interpreted largely as those of omission. Since family members were not questioned directly, a positive family history would be expected considerably more often than actually reported. A rough index of the degree of under-reporting can be calculated from the parent data. One can assume that the incidence of allergy in a total population of parents at a comparable age would have been the same as the overall student incidence, namely, 16.7%. Actually, allergy was reported in 8.1%, only about half that expected (Table IV A). One could reasonably assume that the incidence of recognized allergy in other family members would be even lower.

The incidence of students reporting asthma and/or "hayfever" in our study (16.7%) is somewhat higher than that of other comparable studies. *Jimenez* (1934) reported a 11.9% incidence in University of Michigan students and a little later *Rowe* (1937) found a 13% incidence of asthma and/or "hayfever" in 2000 students. *Ratner and Silberman* (1952) more recently noted a frequency of 13% among a random group of medical personnel. The relatively high frequency of allergy reported by our group is

Table III A: Occurrence of a Positive Family History of Asthma or "Hayfever" Nature of Personal History

	Males	Females	Total
Non-Allergic ("Controls")			
Pos. FH	712 (20.5%)	375 (27.0%)	1087 (22.2%)
Neg.	2749	1011	3760
Total	3461	1386	4847
Asthma			
Pos. FH	37 (41.1%)	12 (42.9%)	49 (41.5%)
Neg.	53	16	69
Total	90	28	118
"Hayfever"			
Pos. FH	243 (53.3%)	148 (61.9%)	391 (56.3%)
Neg.	213	91	304
Total	456	239	695
Asthma and "Hayfever"			
Pos. FH	65 (63.2%)	44 (80%)	109 (69.0%)
Neg.	38	11	49
Total	103	55	158
All allergic groups			
Pos. FH	345 (53.1%)	204 (63.4%)	549 (56.5%)
Neg.	304	118	422
Total	649	322	971

Table III B. Allergy in Immediate Family (Parents and/or Siblings)

	Males		Females		Total	
	Number	% of Total	Number	% of Total	Number	% of Total
Total Allergic students	274	42.2	152	47.2	426	43.9
Students with both asthma and "hayfever"	51	49.5	34	61.9	85	53.8
Non-allergic students	518	15	261	18.8	779	16.1

Table III C: Distribution of Affected Family Members

Personal history / Family history	Mother's side	Father's side	Both sides	Sibs or offspring only	Total
Both asthma and "hayfever"	45	32	21	11	109
% of total	41.3%	29.3%	19.3%	10.1%	
Total allergic	239	168	63	79	549
% of total	43.6%	30.6%	11.5%	14.3%	
Non-allergic, Pos. Fam. Hist.	479	301	69	238	1087
% of total	44.1%	27.7%	6.4%	21.9%	

Table IV A: Incidence of Allergy for Each Parent

	Total number of parents	Parents reported to have asthma or "hayfever"
Total[1] allergic students (971)	1942	383 (19.7%)
Non-allergic students (4847)	9694	563 (5.6%)
All students (5818)	11 636	946 (8.1%)
[1] Students with both asthma and "hayfever"	316	84 (26.6%)

particularly impressive since most of these students have grown up and live in a region where airborne pollen and mold spore concentrations are rarely high and ragweed is non-existent.

There is little reason to include a comprehensive review of previous studies on the genetics of allergic diseases in this paper. Certain noteworthy studies were reviewed and well analysed by *Ratner and Silberman* (1952) and also by *Schwartz* (1952). Our observation that 56.5% of allergic individuals reported a positive family history for asthma or "hayfever" (Table III) agrees quite well with previous studies (Reviewed by *Schwartz*, 1952). Even the earliest reports, by *Cooke and Vander Veer* (1916) and *Rackemann* (1918) indicated a familial incidence close to 50%.

Our finding of 22.2% family allergy in the non-allergic control group is consistent with the other studies on university students (*Jimenez*, 1934, *Rowe*, 1937), though a significantly lower family incidence was recorded in

Table IV B. Frequency of Allergy in Students According to Parental History Alone

	Students		
	Non-allergic	Allergic[2]	% Allergic
Group A, both parents allergic	21 (0.4%)	29 (3.0%)	58.0%
Group B one parent allergic	521 (10.5%)	325 (33.4%)	38.4%
Group C, neither parent allergic	4305 (89.0%)	617 (63.5%)	12.5%

The figures in parentheses indicate the percentage of the total group of students in each category.

[2] Those with both asthma and "hayfever":
Group A: 11 (7.0%)
Group B: 62 (39.2%)
Group C: 85 (53.8%)

earlier studies (*Cooke and VanderVeer*, 1916, *Spain and Cooke*, 1924, *Balyeat*, 1928).

In considering possible genetic mechanisms for transmission of such a common disorder as allergy, one must first rule out the possibility that the observed differences in family history are due to chance alone. If the incidence of asthma and "hayfever" in our group (16.7%) is used as an estimate of that in the general population (including all family members),

Table V. Probability of at Least one Family Member being affected with Asthma or "Hayfever" by Chance alone (Assuming a 16.7% Allergy Incidence)

n	Probability $1-(.833)^n$
1	.17
2	.31
3	.42
4	.52
5	.60
6	.67
7	.72
8	.77
9	.81
10	.84

n: number of known family members

the probability of allergy being reported in at least one person of any given random family becomes impressive, particularly if the number of known members is large (Table V). For example, if each allergic individual knows the medical background of even five family members, the probability of allergy being reported might be 60% on the basis of population incidence alone! This is remarkably close to our observed incidence of 56.5%, and one must then consider the possibility that the low family incidence reported by non-allergic students is due to frequent lack of recognition of existing asthma or "hayfever".

However, certain characteristics of our family data could not be readily explained by chance distribution and vagaries in reporting, and indicated the existence of a genetic influence. The group of persons with both asthma and "hayfever" reported a family incidence of almost 70%; indeed, the females reported 80% (Table IIIA). This group also presented a high incidence when only the immediate family was considered (Table IIIB), and differed significantly from the rest of the allergics (53.8% vs. 41.9%, $\chi^2 = 7.5$, $p = 0.006$). Finally, the percentage of bilateral family involvement was found to be much higher than in other categories (Table IIIC). The difference from non-allergic is highly significant (19.3% vs. 6.4%, $\chi^2 = 17.2$, $p = < 0.0001$) and from other allergic persons is also suggestive (19.3% vs. 11.5%, $\chi^2 = 6.47$, $p = 0.01$).

Further study of the family allergy data of Table III would be unrewarding, since we could make no estimate concerning failure to report existing family allergy, without knowing the total number of relatives for each individual. Since we did not have this information, we used the available data for a family group of known size, namely the parents. Accordingly, attempts to establish the nature of heritability were based largely on the parent data presented in Table IV.

The frequency of allergy in the parents of allergic students is apparently much greater than in the parents of the non-allergic group (19.7% vs. 5.6%, Table IVA). It is conceivable that this marked difference was due to a difference in *recognition* of parent allergy between the two groups, and that heritable factors were not involved. However, the assumption of random distribution would require that 16.7% of parents be allergic. Allergic students reported an incidence significantly greater than this (19.7%, $\chi^2 = 12.9$, $p < 0.0004$). The frequency of parent allergy in the group of students who had had both asthma and "hayfever" was even more impressive (26.6%).

In Table IVB, the data of Table IVA are rearranged and augmented to indicate the frequency of biparental allergy. The differences between the

allergic and non-allergic student groups are again significant, and, the strong influence of family allergy in those students with more severe disease (both asthma and "hayfever") is clearcut.

Since 63.5% of the allergic students reported no parental involvement (Group C, Table IV B), the allergic state could not have been inhertited as a simple fully penetrant dominant character. If the allergic character were fully recessive, all children born of two allergic parents should have allergies. The actual incidence was only 58% (Group A, Table IV B). Accordingly, a more complex genetic mechanism must exist.

Wiener, Zieve and Fries (1936) assumed the presence of one "allergy" gene with incomplete penetrance in the heterozygous state, and full penetrance in the homozygous state, so that allergic subjects would be either heterozygous or homozygous for such a gene. Data then available were interpreted to fit the concept that one-third of allergics were homozygous, that 18% of "heterozygotes" developed allergic disease (18% "penetrance") and that 22% of apparently normal individuals carried the h ("allergic") gene. An important assumption was that all homzygous (hh) allergic persons (one-third) developed symptoms before puberty, the remaining two-thirds of allergics being heterozygous (Hh).

Using the above approach, we calculated the expected gene and genotype frequency in our population by substituting our figure of 16.7% incidence of allergy for the 7% used by *Wiener, Zieve and Fries*. The fraction of allergic persons assumed to be homozygous was arbitrarily varied from

Table VI. The calculated incidence of allergy in offspring of allergic and non-allergic parents assuming that allergy is heritable by an incomplete recessive mechanism. Figures for several possible frequencies of homozygous allergy are presented, with corresponding degrees of penetrance (a 16.7% allergy incidence is assumed, see appendix for method of calculation).

% of allergics homozygous	"Penetrance" in heterozygotes	Percent of offspring allergic		
		Group A Both parents allergic	Group B One parent allergic	Group C Neither parent allergic
10.0%	65.8%	62.9%	38.5%	5.9%
20.0	44.7	57.5	31.9	9.0
33.3	31.0	58.9	29.2	10.1
40.0	26.0	59.9	28.3	10.2
50.0	20.0	64.0	28.0	10.4
70.0	11.1	74.8	27.9	9.9
Observed values		58.0%	38.4%	12.5%

10% to 70% in our calculations. From this information it was possible to calculate[1] the expected incidence of allergy in offspring, assuming random mating (*Kempthorne*, 1957). The results are given in Table VI, for the three combinations of parents. The expected frequency of allergic offspring proved to be relatively constant over a wide range of homozygous allergic frequencies; our observed frequencies (Table IV B) were roughly comparable to values corresponding to an incidence of homozygosity varying from 20% (44.7% penetrance) to 50% (20% penetrance). The observed values for Groups D (38.4%) and C (12.5%) were higher than any calculated values; it is possible to attribute such a finding to the variable underreporting of family allergy, though our data are inadequate to establish this relationship.

Our observations could be interpreted as consistent with the concept of *Wiener, Zieve and Fries* (1936) concerning allergic inheritance by an incompletely recessive gene. Although such a hypothesis is attractive because of its simplicity, the findings on family incidence are equally compatible with a polygenic system determining allergic symptoms (*Penrose*, 1953). In such a system, multiple additive genes would interact in determining susceptibility. The more such genes a person carried, the higher would be his chance of being allergic. In the absence of any quantitative methods for determining the degree of allergy objectively, it is difficult to test this concept specifically.

Accurate measurements related to many variables, such as age of onset, level of external stimuli (including allergenic, irritative and emotional), and the actual degree of hypersensitivity, must be made on both "allergic" and "non-allergic" individuals in considerable numbers before a better estimate can be made concerning the role of heritable factors. The available data provide at best a framework for productive speculation and a pattern for future more objective studies.

Summary

In a study of 5818 college students, 16.7% reported asthma and/or "hayfever". A positive family allergy history was obtained in 56.5% of the allergic group and in 22.2% of the non-allergic students. Parental allergy was found in 19.7% of the allergic group and in 5.6% of the control population.

When both parents were allergic, 58.1% of the offspring were also affected. With one affected parent, 38.4% of the children showed allergy.

[1] Example of calculations (see Appendix).

When both parents were normal, only 12.5% of the offspring were allergic. The presence of both asthma and "hayfever" in the same individual was associated with an especially strong familial background.

These results indicate the role of genetic factors in the pathogenesis of allergy. They could not have occurred by chance alone due to a high population incidence of allergy coupled with under-reporting in the non-allergic population. Genetic analysis indicates that the data are compatible generally with Wiener's hypothesis of an incompletely recessive gene for allergy. However, a polygenic system determining allergic susceptibility could explain the results equally well.

Zusammenfassung

Eine Untersuchung von 5818 College-Studenten ergab bei 16,7% Asthma und/oder Heuschnupfen. Eine positive Familiengeschichte in bezug auf Allergie fand sich bei 56,5% der allergischen Gruppe und bei 22,2% der nicht allergischen Studenten. Allergie der Eltern wurde in der allergischen Gruppe bei 19,7% gefunden und bei 5,6% der Kontrollgruppe.

Waren beide Eltern allergisch, so übertrug sich das auf 58,1% der Nachkommen. Bei einem allergischen Elternteil zeigten 38,4% der Kinder allergische Erscheinungen. Waren beide Eltern normal, so waren nur 12,5% der Nachkommen allergisch. Asthma und Heuschnupfen zusammen traten vorwiegend bei solchen Individuen auf, deren Vorfahren eine besonders starke familiäre Belastung aufwiesen.

Die Ergebnisse zeigen, welche Rolle genetische Faktoren in der Pathogenese der Allergie spielen. Es kann sich dabei nicht um ein Zufallsergebnis handeln, das etwa durch ein häufiges Vorkommen der Allergie in der Bevölkerung in Verbindung mit unvollständiger Berichterstattung bei den allergischen Kontrollen bedingt wäre. Die genetische Analysis zeigt, daß die Daten im allgemeinen mit *Wieners* Hypothese eines unvollständig rezessiven Gens für Allergie übereinstimmen. Jedoch könnte ein polygenes System, das die Anfälligkeit für Allergie bedingt, die Ergebnisse genau so gut erklären.

Résumé

Dans une étude de 5818 collégiens, l'auteur a trouvé 16,7% de cas d'asthme et/ou de rhume des foins. 56,5% des cas du groupe allergique et 22,2% des étudiants non allergiques révélaient une histoire familiale positive d'allergie. Une allergie des parents se rencontrait dans le 19,7% du groupe allergique et dans le 5,6% de la population témoin.

Lorsque les deux parents étaient allergiques, 58,1% des enfants étaient également affectés. Lorsque seulement un des parents était atteint, 38,4% des enfants présentaient une allergie. Si les deux parents étaient normaux, seul le 12,5% de la descendance était allergique. L'association d'asthme et de rhume des foins dans le même individu indiquait toujours une hérédité familiale très chargée.

Ces résultats démontrent le rôle des facteurs génétiques dans la pathogénèse de l'allergie. Il n'est pas possible de les expliquer uniquement par un hasard dû à la fréquence accrue d'allergie dans la population en général d'une part, et à une sous-estimation de son incidence réelle dans la population non allergique d'autre part. Il ressort d'une analyse génétique que les résultats obtenus correspondent bien à l'hypothèse de *Wiener* d'un gène incomplètement récessif pour l'allergie. Cependant, un système polygénique responsable de la susceptibilité allergique pourrait également expliquer ces résultats.

REFERENCES

1. *Balyeat, R. M.:* The hereditary factor in allergic diseases. Amer. J. med. Sci. *176:* 332–345 (1928).
2. *Cooke, R. A. and Vander Veer, A. Jr.:* Human sensitization. J. Immunol. *1:* 201–305 (1916).
3. *Jimenez, B.:* A survey of sensitization in students of the University of Michigan. J. Mich. State med. Soc. *33:* 310–312 (1934).
4. *Kempthorne, O.:* An introduction to genetic statistics; ch. 2 (Wiley, New York 1957).
5. *Penrose, L. S.:* The genetical background of common diseases. Acta genet. *4:* 257–265 (1953).
6. *Rackemann, F. M.:* A clinical study of one hundred and fifty cases of bronchial asthma. Arch. intern. Med. *22:* 517–552 (1918).
7. *Ratner, B. and Silberman, D. E.:* Allergy – its distribution and hereditary concept. Ann. Allergy *9:* 1–20 (1952).
8. *Rowe, A.:* Clinical allergy; pp. 23–24 (Lea and Febiger, Philadelphia 1937).
9. *Schwartz, M.:* Heredity in bronchial asthma (Munksgaard, Copenhagen 1952).
10. *Spain, W. C. and Cooke, R. A.:* Studies in specific hypersensitiveness. J. Immunol. *9:* 521–569 (1924).
11. *Wiener, A. S.; Zieve, I. and Fries, J.:* The inheritance of allergic disease. Ann. Eugen. *7:* 141–162 (1936).

ACKNOWLEDGEMENTS

We are grateful to Dr. Gordon Bergy, Director of the Hall Health Center, University of Washington, and his staff, for their constant cooperation.

Authors' address: Dr. P. P. VanArsdel Jr. and Dr. A. G. Motulsky, Dept. of Medicine, University of Washington, School of Medicine, *Seattle 5*, Wash. U.S.A.

Appendix

Example of Calculations Used for Obtaining Data for Table VI.

Observation – 16.7% allergy incidence

Assumption – $\frac{1}{3}$ of allergics homozygous (hh)

Therefore, $\frac{16.7}{3} = 5.6\%$ of total population hh

$16.7–5.6 = 11.1\%$ of total population Hh allergic (heterozygous)

Frequency of gene h $= \sqrt{.056} = 0.236$

Therefore frequency of gene H $= 1-.236 = 0.764$

Frequency of HH $= (.764)^2 = 0.584$

So, frequency of Hh $= 1-(.584+.056) = 0.360$

Since Hh (allergic) frequency $= 0.111$

Then Hh (non-allergic) frequency $= 0.249$

$$\text{Penetrance} = \frac{\text{Hh(allergic)}}{\text{Hh (total)}} = \frac{0.11}{0.36} = 31\%$$

With both parents allergic:

Then phenotype distribution $= .33$ hh $+ .67$ Hh
and gene frequency is $.67$ h $+ .33$ H

Phenotype distribution in offspring $= (.67\text{ h} + .33\text{ H})^2$
$= .45$ hh $+ .45$ Hh $+ .11$ HH

Allergics: $= .45 + (.45)\ (.31) = 59\%$

If one parent is non-allergic:

Non-allergic phenotype distribution $= .3$ Hh $+ .7$ HH
and genotype distribution $= .15$ h $+ .85$ H

Offspring phenotypes $= (.67\text{ h} + .33\text{ H})\ (.15\text{ h} + .85\text{ H})$
$= .10$ hh $+ .62$ Hh $+ .28$ HH

Allergic frequency $= .10 + (.62)\ (.31) = 29.2\%$

Neither parent allergic:

Offspring phenotypes $= (.15 + .85\text{ H})^2$
$= .02$ hh $+ .26$ Hh $+ .72$ HH

Allergic frequency $= .02 + (.26)\ (.31) = 10.1\%$

Identical results were obtained when all possible mating patterns were tabulated and the offspring divided into the various phenotypic categories.

Roos, J. and Huizinga J.: Acta genet. 9 : 115—122 (1959)

From the University Hospital, Medical Dept., Utrecht, and the State University of Utrecht, Dept. of Physical Anthropology and Human Genetics: Anatomical Laboratory; Utrecht, Holland

GENETIC INVESTIGATION OF THE STUART COAGULATION DEFECT

By J. ROOS and J. HUIZINGA

In 1952 *van Belle* described a Dutch family (the K. family; fig. 1) in which a congenital haemorrhagic diathesis occurred in 6 out of 12 children. A 13th child had died in childhood. The parents appeared to be first cousins.

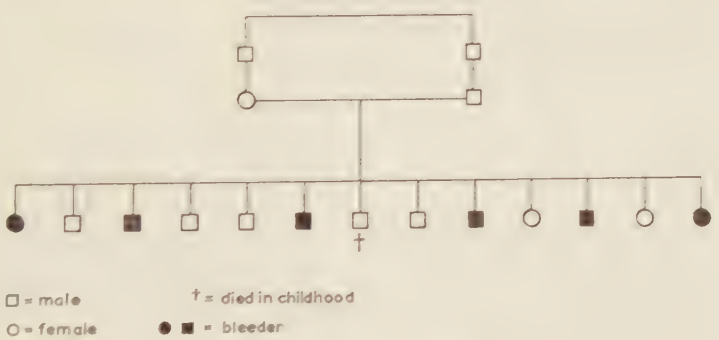


Fig. 1 The K. Family

The bleeding tendency manifested itself in long lasting nose and mucosal haemorrhages, spontaneous skin haemorrhages, menorrhagias, haematurias and probably (in one case) haemarthros. *Van Belle* ascribed this haemorrhagic diathesis to a lack of proconvertin (factor VII): this factor had been described somewhat earlier (1951) by *Alexander*. Blood

coagulation studies in the 6 normal children, both parents and in some relatives did not reveal any disturbances.

Now, it has been found during the last few years that those who had been considered to suffer from proconvertin deficiency are to be divided into two groups. The blood of some patients failed to correct (in vitro) the deficit in *Alexander*'s patient; they are considered to suffer from the same coagulation defect. The blood of the other patients, on the contrary, is able to perform this correction. The factor considered to be deficient in these patients is referred to as Stuart factor, after the surname of the first described patient (*Hougie et al.;* 1957).

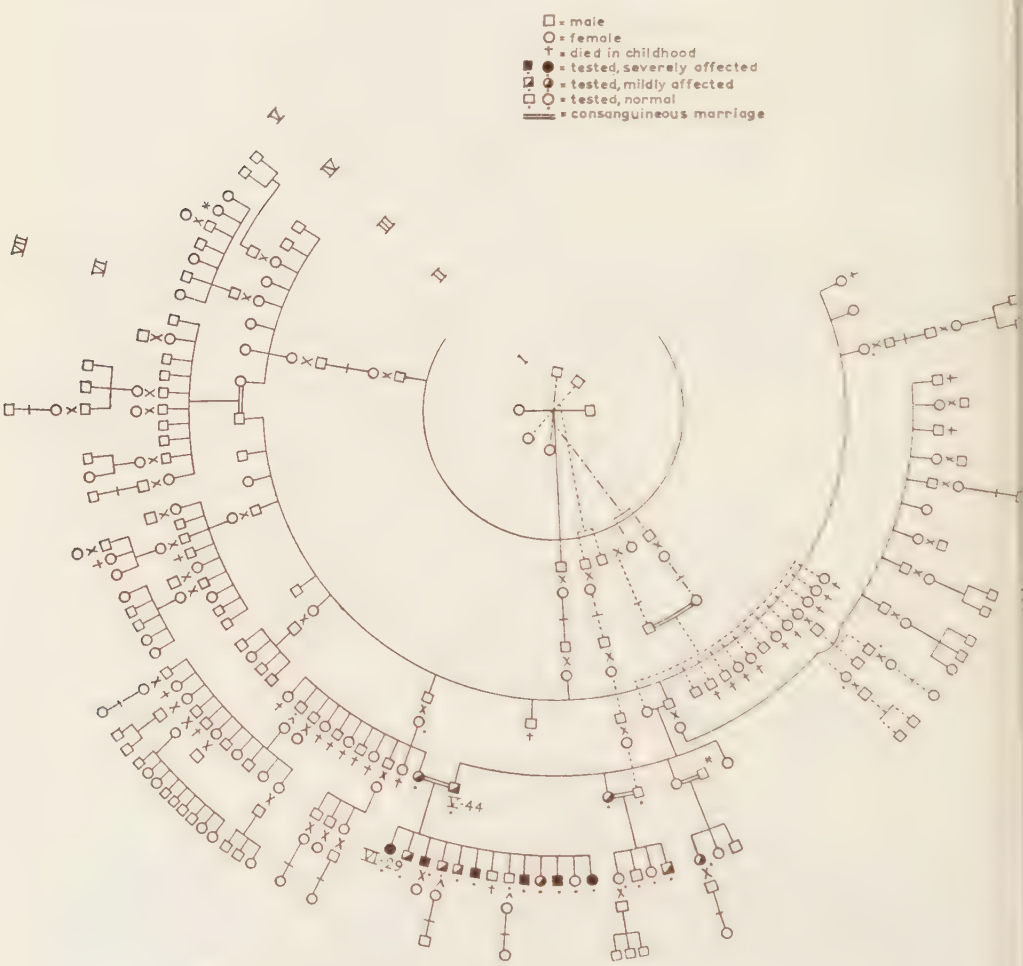


Fig. 2 The K. pedigree *($V_5 = V_{48}$) VI-29 = III-1 in Fig. 1

Moreover, these two groups of patients differ in capacity to form blood thromboplastin; in patients of the first group, suffering from the "true" factor VII deficiency, the generation of blood thromboplastin is normal, while in patients belonging to the Stuart group, this generation is defective (*Bachmann et al.*; 1957).

Repeated investigation of the patients described by *van Belle* revealed that their haemorrhagic diathesis resulted from a Stuart factor deficiency (*Roos et al.*, 1959).

Except in the 6 bleeders, coagulation studies could be performed in 20 clinically healthy relatives of the patients (fig. 2), including both parents and 6 siblings. The distribution of the Stuart factor values found in the 26 cases (determination according to *Bachmann*'s method 3; 1957) is given in fig. 3, together with similar values determined in 18 normal controls not belonging to this family. In the 6 bleeders the Stuart factor "content" was found to vary between 5.0 and 6.2%.

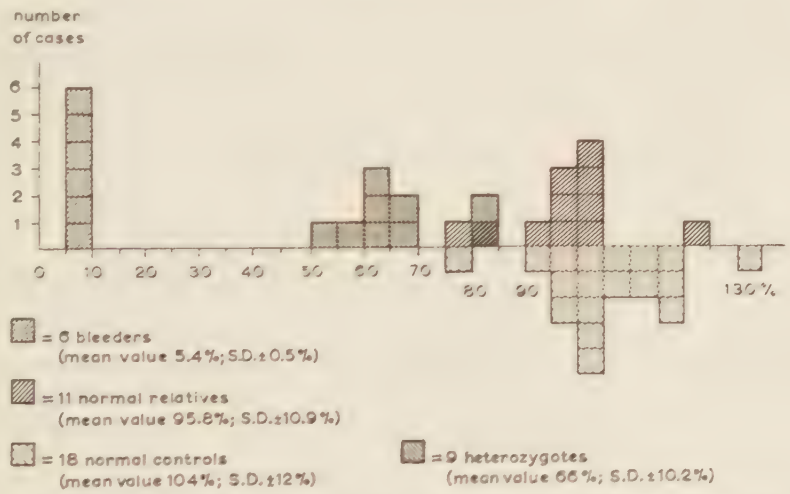


Fig. 3 Concentration of Stuart factor in bleeders, their relatives and normal controls.

The distribution of the Stuart values in the 20 relatives investigated points to the possibility of distinguishing two groups of values:

a) eleven individuals whose Stuart "content" ranges from 75% to 120% (mean value 95,8%; $\sigma \pm 10{,}9\%$). The mean value found in 18 normal controls amounts (in our laboratory) to 104% ($\sigma \pm 12\%$). There is no reason to consider these two means to differ significantly ($0.05 < P < 0.100$), especially not if one only considers those 10 individuals whose values range

between 80% and 128%. The question whether also the 11th case of this group, that with a Stuart value of 75%, should be taken as normal, will be dealt with later on.

b) nine individuals whose Stuart values vary between 50% and 82% (mean value 66%; $\sigma \pm 10{,}2\%$). The difference between the mean values of groups a and b respectively is undoubtedly of significance ($P \leqslant 0{,}001$).

The investigated individuals are entered in fig. 2 with the aid of symbols (severely affected: the 6 bleeders; mildly affected: the 9 individuals of group b; normal: the 11 cases belonging to group a).

The classification of the "borderline cases" among the 20 individuals investigated (75%; 80%; 82%; 82%) as given in fig. 3 is also based on the results of investigations into other aspects of the Stuart factor deficiency (one stage "prothrombin" time with human brain thromboplastin or Russell's viper venom-cephalin; factor VII content; correction of the thromboplastin generation test of the bleeders by the tested sera). These results have been dealt with in detail previously (*Roos et al.*; 1959).

Reports on the genetic aspects of this rather "new" haemorrhagic diathesis are extremely scarce. In 1957 *Graham et al.* described the original Stuart pedigree in which one severe bleeder occurred (fig. 4). His very low

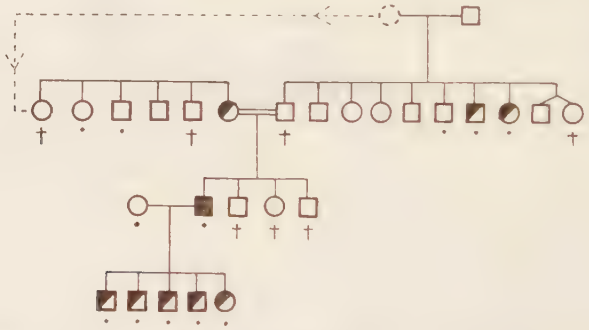


Fig. 4 Part of the Stuart pedigree (after *Graham, Barrow* and *Hougie;* 1957)

level of Stuart factor contrasted with that of normals (members of the family) and with that of a group of relatives showing Stuart values somewhat between those of the normals and that of the patient. It was hypothesized that the proband would be homozygous for an abnormal autosomal gene, that the possessors of intermediate values of Stuart factor would be heterozygous for this gene, and that the "normals" would be homozygous normal.

The analysis of the pedigree did not reveal facts inconsistent with this hypothesis. The observation by *Crockett et al.* (1949) of a female patient probably suffering from Stuart factor deficiency (as shown by *Hougie et al.;* 1957) lends support to the hypothesis of *Graham et al.*, as her father, mother and sister appeared normal clinically. *Bachmann et al.* (1957) stated that in their case of Stuart factor deficiency (Delia B.) the mode of inheritance of this condition was "an intermediate autosomal one". In 1958 the relevant pedigree was demonstrated (Rome; 7th Congress on Haematology). It was pointed out that clinically the Stuart factor deficiency "seems to be inherited as a recessive characteristic". However, "the use of a specific assay method allows to detect the heterozygotes without manifest bleeding tendency".

Now, it remains to be examined whether our family investigations are consistent with the hypothesis of *Graham et al.*[1] If we assume the pathological gene leading to Stuart factor deficiency to be present in heterozygous condition in *both* parents of the bleeders as a consequence of their being first cousins, this mating may be described as St.st. x St.st. It may be expected, then, that the distribution of the genotypes St.St., St.st. and st.st. among the children of these parents resembles the ratio 1:2:1. The level of Stuart factor could be determined in 12 out of the 13 children resulting from the marriage. Among these 12 siblings the distribution of the genotypes mentioned, as judged from the levels of Stuart factor and some additional data, appears to be 6 homozygous abnormals (st.st.) against 4 heterozygotes (St.st.) and 2 genetic normals (St.St.). In the same order the expected numbers amount to 3, 6 and 3.

In this sibship of 12 the chance of i sibs being homozygous abnormal (st.st.), while, at the same time, j of the remaining 12-i individuals are heterozygous (St.st.) and, thus, 12-i-j sibs homozygous normal (St.St.) may be written as

$$\left\{\binom{12}{i}\left(\tfrac{1}{4}\right)^{i}\left(\tfrac{3}{4}\right)^{12-i}\right\} \cdot \left\{\binom{12-i}{j}\left(\tfrac{2}{3}\right)^{j}\left(\tfrac{1}{3}\right)^{12-i-j}\right\}$$

$$\text{or} \quad \binom{12}{i} \cdot \binom{12-i}{j} \cdot \left(\tfrac{1}{2}\right)^{24-j}$$

It may be calculated that the chance of finding exactly the distribution 3:6:3 of the relevant genotypes in this sibship only amounts to .0705, i.e. $\approx 7\%$.

[1] Thanks are due to Mr. J. A. van der Heiden, statistician Koninklijke Shell/The Hague, for his helpful advice and criticisms.

i \ j	0	1	2	3	4	5	6	7	8	9	10	11	12
0	.0000	.0000	.0000	.0001	.0005	.0015	.0035	.0060	.0076	.0067	.0040	.0015	.0002
1	.0000	.0000	.0002	.0009	.0038	.0106	.0211	.0302	.0302	.0201	.0080	.0015	
2	.0000	.0001	.0007	.0038	.0132	.0317	.0529	.0604	.0453	.0201	.0040		
3	.0000	.0002	.0019	.0088	.0264	.0529	.0705	.0604	.0302	.0067			
4	.0000	.0005	.0033	.0132	.0330	.0529	.0529	.0302	.0076				
5	.0000	.0007	.0040	.0132	.0264	.0317	.0211	.0060					
6	.0000	.0007	.0033	.0088	.0132	.0106	.0035						
7	.0000	.0005	.0019	.0038	.0038	.0015							
8	.0000	.0002	.0007	.0009	.0005								
9	.0000	.0001	.0002	.0001									
10	.0000	.0000	.0000										
11	.0000	.0000											
12	.0000												

i = number of homozygous abnormals
j = number of heterozygotes

Fig. 5 Probability of any i/j-combination in a sibship of 12

The chance occurrence of all possible i, j-combinations in this sibship has been calculated. For the benefit of those who may investigate a sibship of 12 in which the present situation also arises the figures obtained are given in fig. 5.

Now, with the aid of this trinomial distribution it can be found whether the actual distribution of genotypes 6:4:2 differs considerably from the distribution expected on the basis of the hypothesis of *Graham et al.* (3:6:3), or whether the differences may be due to random circumstances.

Just as in the case of the ordinary binomial distribution the chances representing the "rare occurrences" must be added (in their order of ranking) to that level that in a certain case is considered to represent the "level of significance". Usually .05 (5%) is taken for this level. In this way in a symmetrical binomial distribution two symmetrically placed areas, each comprising occurrences up to a total of 2½%, are found. In the present case of a trinomial distribution the area covering the "rare occurrences" is of a rather complicated form.

Fig. 5 shows that the combination of genotypes found in our family K. ($i = 6, j = 4$) does not belong to those occurrences covered by the 5% area. We may go further and limit the 10% area; even then the combination found may still be in accordance with *Graham et al.*'s hypothesis.

Thus, it was found that the discrepancy between observed and expected numbers of the 3 genotypes in our family easily may be due to chance ($\cdot 10 < P < \cdot 15$). Therefore, there is no reason to reject the hypothesis that the occurrence of the Stuart factor deficiency depends on the presence of a mutant gene which, when represented once in the genetic make up (heterozygous state) is responsible for a deficit detectable by laboratory methods, but, when represented twice (homozygous condition) leads to the clinically serious form of deficiency.

It should be noted that in our case the mean Stuart value in heterozygotes is *not* exactly intermediate between the means of the two groups of homozygous individuals (normals and bleeders). Even in case the Stuart gene concerned would have a purely quantitative effect, it should not be expected that the "double quantum" in homozygous individuals leads to Stuart values twice those found in heterozygotes. For this "value" is determined only by the rate of appearance of a fibrin clot in the test tube, using the proper reaction mixture. The 5% value still found in homozygous abnormals (lacking the normal genes!) also should be considered from this point of view.

Summary

The analysis of a pedigree in which a particular disturbance of blood coagulation occurred (Stuart deficiency) revealed no inconsistencies with the hypothesis given by *Graham et al.*: the haemorrhagic diathesis is based on the presence of a mutant gene in homozygous condition. The heterozygous condition may be detected by laboratory methods.

Zusammenfassung

Die Analyse eines Stammbaumes, in dem eine gewisse Blutgerinnungsstörung auftrat (Stuart-Defekt), zeigte keine Abweichungen von der von *Graham* aufgestellten Hypothese. Die hämorrhagische Diathese beruht auf dem Vorhandensein eines mutierten Genes in homozygotem Zustand. Der heterozygote Zustand kann mit Hilfe von Laboruntersuchungen festgestellt werden.

Résumé

L'analyse de l'arbre généalogique dans lequel se manifeste un trouble particulier de la coagulation du sang (Stuart défaut) n'a pas révélé d'incompatibilité avec l'hypothèse de *Graham et coll.*: la diathèse hémorragique est due à la présence d'un gène muté dans l'état homozygote. L'état hétérozygote peut être mis en évidence par des méthodes de laboratoire.

REFERENCES

1. *Alexander, B.; Goldstein, R.; Landwehr, G. and Cook, C. D.:* Congenital SPCA-deficiency. J. clin. Invest. *30:* 596 (1951).
2. *Bachmann, F.; Duckert, F.; Geiger, M.; Baer, P. and Koller, F.:* Differentiation of the Factor VII Complex. Thromb. Diath. haem. *1:* 169 (1957).
3. *Bachmann, F. and Anders, G.:* Family investigations in a case of congenital Stuart-Prower factor deficiency. VIIth Congr. Intern. Soc. haemat., Rome 1958, p. 459.
4. *Belle, C. J. van:* Parahaemophilie. Thesis (Utrecht 1952).
5. *Crockett, C. L.; Shotton, D.; Craddock, C. G. and Leavell, B. S.:* Hypoprothrombinemia: studies of a case of the idiopathic type and the effect of serum administration. Blood *4:* 1298 (1949).
6. *Graham, J. B.; Barrow, E. M. and Hougie, C.:* Stuart clotting defect. II. Genetic aspects of a "new" hemorrhagic state. J. clin. Invest. *36:* 497 (1957).
7. *Hougie, C.; Barrow, E. M. and Graham, J. B.:* Stuart clotting defect. I. Segregation of an hereditary hemorrhagic state from the heterogenous group heretofore called "stable factor" (SPCA) deficiency. J. clin. Invest. *36:* 485 (1957).
8. *Roos, J.; van Arkel, C.; Verloop, M. C. and Jordan, F. L. J.:* A "new" family with Stuart-Prower Deficiency. Thromb. Diath. haem. *3:* 59 (1959).

Authors' addresses: Dr. J. Roos, Medical Dept., University Hospital, *Utrecht*, and Dr. J. Huizinga, Dept. of Physical Anthropology and Human Genetics; Anatomical Laboratory; State University of *Utrecht* (Holland).

Milch, R. A.: Acta genet. *9*: 123—126 (1959)

Division of Orthopaedic Surgery, The Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Baltimore, Maryland.

A PRELIMINARY NOTE OF 47 CASES OF ALCAPTONURIA OCCURRING IN SEVEN INTERRELATED DOMINICAN FAMILIES, WITH AN ADDITIONAL COMMENT ON TWO PREVIOUSLY REPORTED PEDIGREES[1]

By ROBERT AUSTIN MILCH

Alcaptonuria, a genetically determined "inborn error of metabolism" characterized by the abnormal urinary excretion of homogentisic (2,5-dihydroxyphenylacetic) acid, has been accepted generally as if inherited in consequence of a rare, simple, autosomal recessive gene substitution (1). Attention has been directed elsewhere (2, 3, 4), however, to the alternate possibilities that the gene may behave as a dominant "in a restricted range of variation", or may co-exist with an additional pair of gene factors to produce an apparent incompletely penetrant dominant gene substitution. Although this latter view has the merit of incorporating data explained by both the simple recessive and the simple dominant hypotheses, sufficient data have not been presented by this or other writers to justify either its unequivocal acceptance or rejection. More extensive study, therefore, appeared to be indicated.

The fact that both the family reported by *Pieter* (1925), which is generally accepted as the single unequivocal instance of a dominant pattern of inheritance in the literature, and that reported by this writer (1955, 1957) derived from the same geographical area (Dominican Republic), suggested

[1] Aided by a grant (A-2642) to the Johns Hopkins University from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, United States Department of Health, Education and Welfare.

the obvious possibility that the two might actually be inter-related. Accordingly, an investigation has been conducted of all known members of the two families.

A large number of individuals in seven different, but highly inter-related families have been questioned and examined both clinically and chemically for the presence and stigmata of homogentisic aciduria. A detailed analysis of the family inter-relationships will be published separately. It is significant, however, to call attention here to certain newly discovered data, particularly insofar as they relate to previously published material.

In the first place, two errors in the original pedigree published by this writer have been uncovered which tend almost entirely to invalidate the suggested possibility of the two gene hypothesis. One subject (III-3 of family 3) in the pedigree (Fig. 1), previously reported to have alcaptonuria, has been examined and has been found to be non-alcaptonuric. The status of II-1 in the same pedigree, previously believed to have been alcaptonuric, now appears to be subject to some doubt, though the weight of current indirect evidence would tend to suggest that this individual likewise did not have alcaptonuria. This individual had been deceased for several years at the time the pedigree was first published (5) and data concerning his

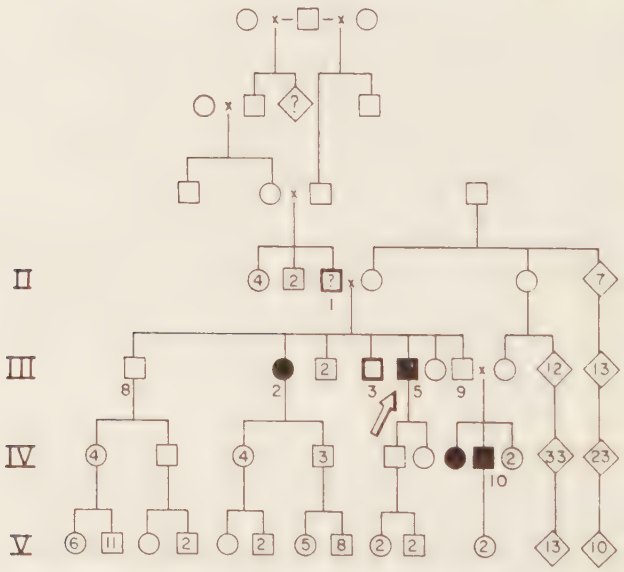


Fig. 1 Corrected and expanded pedigree of family 3 of the initial report (Acta Genetica, 7:178, 1957) using the same system of identification. II-1 is probably non-alcaptonuric and III-3 is normal.

status as regards alcaptonuria had previously been obtained but from a single individual. Additional members of the family fail, however, to remember any of the stigmata of homogentisic aciduria in this subject, and hence he is now considered to have been normal.

In the second place, it appears that the antecedents of this family are in fact the antecedents of the family reported by *Pieter*. Inter-reationships between the two families extending for a total of eight generations, and involving five other inter-related families as well, have been ascertained and a great number of additional cases of alcaptonuria discovered.

Forty alcaptonuric subjects previously unknown to the medical literature have been positively identified. An additional two patients with positive clinical and laboratory evidence of alcaptonuria, who may have been included in the pedigree reported by *Pieter*, have also been discovered. Another subject, who has all of the clinical and chemical features of the alcaptonuria syndrome, has been interviewed through a third party, though has not been examined personally. An additional 2 individuals known to be alcaptonuric live in a small rural community which is densely populated with alcaptonurics, but they could neither be interviewed nor their relationship established with respect to other members of the study families.

It would appear, therefore, when the four unequivocal cases previously noted are included, that at least 47 and probably 49 cases of alcaptonuria have been demonstrated to occur within eight generations of seven highly inter-related families in the Dominican Republic.

Preliminary examination of the large pedigree constructed on the basis of all currently available data would tend to suggest that alcaptonuria is inherited in these highly inter-related families as if in consequence of the action of a simple recessive gene substitution. This would appear to be in accord with the vast majority of the data in the literature, despite the appearance of several instances of direct inheritance from parent to offspring in these pedigrees.

Summary

A study has been undertaken of a large number of persons among eight generations of seven highly inter-mated families residing in the Dominican Republic. Data have been obtained to indicate that previously presented information concerning this family is in part incorrect. The pedigree has been corrected and considerably lengthened to include 47 cases. Of this number, 42 (and probably 43) are newly discovered and unreported cases.

The corrected and partially expanded pedigree relevant to family 3 of the initial report is presented. It is suggested that alcaptonuria is inherited

as if in consequence of a simple, autosomal recessive gene substitution. A detailed account of the families will be presented elsewhere[2].

Zusammenfassung

Eine große Anzahl von Personen wurde untersucht, die aus 8 Generationen von 7 in der Dominikanischen Republik lebenden, eng miteinander verwandten Familien stammen. Wie die Ergebnisse zeigen, waren frühere Angaben über diese Familien zum Teil nicht korrekt. Der Stammbaum wurde dementsprechend geändert und erheblich erweitert und umfaßt jetzt 47 Fälle. Davon sind 42 (wahrscheinlich sogar 43) neu entdeckte und vorher nicht erwähnte Fälle.

Der geänderte und teilweise ergänzte Stammbaum der Familie 3 des ursprünglichen Berichtes wird dargestellt. Die Beobachtungen legen die Hypothese nahe, daß die Alcaptonurie einfach autosomal rezessiv vererbt wird. Ein ausführlicher Bericht über diese Familien wird anderswo gegeben werden.

Résumé

Plusieurs personnes appartenant à 8 générations d'une famille, liées entre elles par de nombreux mariages et habitant la République de St-Domingue ont été étudiées. Il s'est avéré que les informations publiées antérieurement au sujet de cette famille sont en partie incorrectes. L'arbre généalogique a été corrigé et considérablement élargie, puisqu'il comprend maintenant 47 cas. Parmi ceux-ci 42 (et probablement 43) sont des cas nouvellement découverts et pas encore publiés jusqu'à présent.

L'auteur expose l'arbre généalogique corrigé et en partie élargie de la famille 3 de la première communication. Il pense que la transmission héréditaire de l'alcaptonurie correspond à l'effet d'un gène autosomal récessif simple. Un raport détaillé concernant ces familles sera publié ailleurs.

REFERENCES

1. *Garrod, A.E.:* Inborn errors of metabolism. (H. Frowde, Hodder and Stoughton, London, 1923).
2. *Pieter, H.:* Une famille d'alcaptonuriques. Presse méd. *33:* 1310 (1925).
3. *Hogben, L.; Worral, R.L. and Zieve, I.:* The genetic basis of alcaptonuria. Proc. roy. Soc. Edinb. B *52:* 264 (1932).
4. *Milch, R.A.:* Direct inheritance of alcaptonuria. Metabolism *4:* 513 (1955); *Milch, R. A. and Milch, H.:* Dominant Inheritance of Alcaptonuria, Acta genet. *7:* 178 (1957).
5. *Milch, H. and Milch, R.A.:* Alcaptonuria. J. int. Coll. Surg. *15:* 669 (1951).

Author's address: Dr. R. A. Milch, M. D., Division of Orthopaedic Surgery, The Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, *Baltimore* 5, Md. (U.S.A.)

[2] Annual meeting, American Society of Human Genetics, State College, Pa., U.S.A., August 31–September 2, 1959.

Stevanović, D. V.: Acta genet. 9: 127—132 (1959)

From the Department of Dermatology and Venerology.
Medical Faculty, University of Belgrade (Head: Prof. S. Ilic M. D.)

ALOPECIA CONGENITA

The incomplete dominant form of inheritance with varying expressivity.

By DANILO V. STEVANOVIĆ

Congenital alopecia (C.a.) alone, or associated with some other ectodermal defects, has been the subject of number of articles. The condition is known to be inherited either as a dominant or a recessive. Contrary to the fact that a genodermatose inherited as a recessive has more growths (ectodermal or mesodermal) affected and a worse prognosis than its corresponding dominant form, c.a. of the recessive type is usually characterized only by the absence of scalp hair, hair of the other hairy regions being scanty and occasionally absent. This form is represented chiefly by solitary cases and several affected persons occurring in a few families.

In c.a. of the dominant type, however, besides the absence of hair, some other ectodermal growths such as nails, teeth, sebaceous and sweat glands have also been found to be defective. Nails are usually thin, thick or brittle; teeth underdeveloped, dentated, and irregularly arranged.

Disturbances of the keratinization can also be associated with c.a.

The complete absence of the sweat apparatus and a marked intolerance to heat with a few of the above mentioned features are found in the clinical picture of "major ectodermal defects".

Mesodermal defects in patients with a.c. have also been reported and compiled by *Touraine* (1a).

Cases in which hypotrichosis, instead of a total congenital alopecia is present, obey the same laws of inheritance.

Both male and female patients seem to be equally affected. In one family (2), however, the condition was linked to the male sex and dominant, while in another 2, (3, 4) it was recessive, also linked to the male sex. *Cockayne* (5) thought that the family reported by *Sobajima* (4) might in fact be an example of ectodermal anhidrotic dysplasia, the inheritance of which is also sex linked and recessive in character. *Touraine* (1b), however, quoted this family as an example of the translocation of the gene and its subsequent fixation to the sex chromosome, thus explaining sex linkage found in this family.

The association of different clinical features in some members of our family may be of interest both from the genetic and dermatologic point of view.

Report of a family

According to the information obtained from the proband, his grandmother had marked diffuse hyperkeratosis of the palms of hands and soles of feet associated with nail changes. He does not remember whether her eyebrows were lacking, but he remembers well that her scalp hair was normal.

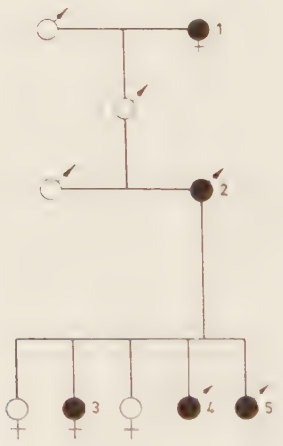


Figure 1. 1. Diffuse keratoderma of palms and soles associated with nail changes. 2. Hypotrichosis of the scalp hair, absence of eyelashes and eyebrows, nail changes, striated keratoderma of palms. 3. Eyebrows and eyelashes absent, nail changes, diffuse keratoderma of palms and soles. 4. Congenital alopecia of scalp hair, absence of eyelashes and eyebrows, nail changes, incipient diffuse keratoderma of palms and soles. 5. Congenital alopecia of scalp hair, absence of eyelashes and eyebrows, nail changes.

The proband's father did not have any changes on the skin.

The proband, R.P., aged 35, a clerk, was born at term with a normal delivery. His scalp hair was always rarified, eyelashes and eyebrows were lacking. He had no need to shave. Hyperkeratosis of the palms and soles was noticed only 3–4 years ago.

On objective examination his scalp hair was rarified, his eyelashes and eyebrows absent. There were also only a few hairs in the axillae and pubic region. Structurally, the hairs did not show any abnormality. Nail plates were dystrophic, covering only half of the normal nail-bed, with their proximal parts hyperkeratotic and brittle (Fig.2).

On both palms there was band-like hyperkeratosis which also extended slightly to the first phalanges of some fingers (Fig.3). The soles were diffusely hyperkeratotic, the part of the sole not touching the ground in walking not being affected. Teeth were normal.

His daughter, now aged 7 (R.N.), was also born at term as were all other affected members, with a normal delivery. Her scalp hair was present at birth and has remained ever since. Her eyelashes and eyebrows have always been absent, and the nails dystrophic. Although hyperkeratosis of

Figure 2. For the explanation see the text.

Figure 3. Striated keratoderma of palms (Brünauer-Fuhs). Keratoderma of soles is diffuse in character.

Figure 4. The appearance of soles in the members (3) of the family.

the palms and plants was not present at birth, it appeared within the first few years of life.

On objective examination, her scalp hair was normal, eyelashes and eyebrows absent. Her nails, like those of her father and other affected members, were dystrophic (Fig. 2). Both palms and soles were diffusely thickened, hyperkeratosis being limited only to these sites and ending abruptly at the margins. (Fig. 4). The teeth were normal.

In both sons, now aged 3,5 (R.R.) and 2 (R.C.) years respectively, there was a complete absence of scalp hair since birth. Eyelashes and eyebrows were also absent; no lanugo hair could be seen.

In the older son (R.R.) keratodermia of the palms and soles identical to that of his sister (R.N.) was also present. It was, however, less pronounced. The nail changes of both brothers were similar to those of the other affected members of the family.

Discussion

We have already mentioned that with the exception of 3 families (2, 3, 4), the condition affects both sexes with the same intensity. *Schultz* (6) reports a brother and 2 sisters who have been completely bald since birth.

Although sex linkage was not observed in our family, the expressivity of the abnormal gene varied according to the sex, in the female sex not affecting scalp hair, in the male sex, on the other hand, giving alopecia. Thus an inhibitory action of the female sex chromosome can be suspected in the female sex only. This inhibitory action, however, was completely manifested for the scalp hair only, other ectodermal growths being equally affected in both sexes. The same inhibitory influence of the female sex chromosome could also be used as an explanation of the unequal distribution of the affection between the two sexes. Although it may be purely due to chance, it is interesting to note that among altogether 3 female siblings, only one was incompletely affected, while both male siblings exhibited complete alopecia.

Sexual predominance of the male sex in our cases hardly comes into question since the relative limitation of the condition observed here (sexual predominance) refers only to the sex and not to the clinical features which are equally expressed in both sexes.

We should also like to repeat here that the proband's wife, as all other members of her paternal and maternal family, were normal.

Beside the expressivity, the incomplete dominant inheritance was also observed in our family, the condition skipping one generation and appearing in the next. The father of the proband must be regarded as a carrier, since both generations, before and after his own, were affected.

Different types of keratodermas have been frequently reported in association with some other ectodermal defects. Two different types occurring in the same person (7) or in the same family (8) have also been reported. Congenital alopecia has been reported so far only in association with circumscribed (9) and diffuse keratodermia *(Unna-Thost)* (10).

The interesting point of our observation lies in the occurrence of 2 different types of keratodermia - viz. diffuse *(Unna-Thost)* and striated *(Brünauer-Fuhs)* in 2 members of our family.

The appearence of 2 different types of keratodermia in the same family suggests their close relationship. Diffuse keratoderma of the Unna-Thost type, as also e.a. in our family, is inherited in a dominant manner, appearing early in life, a fact found also in 2 members (R.R. and R.N.) of our family. The Brünauer-Fuhs type has a later onset (10), which was also

observed in another member of the family (R.P.). There is, however, no full agreement as to the mode of inheritance for this type. *Cockayne* (5) suggested it to be inherited as a simple dominant while *Siemens* (8) thought it to be an example of polymeria. Our observation would also support the latter assumption.

Summary

The family presented here offers an example of a.c. inherited as an incomplete dominant of varying expressivity, associated to keratodermas both of the simple dominant and polymeric character.

Zusammenfassung

Die hier dargestellte Familie bietet ein Beispiel für Alopecia congenita mit unvollständig dominantem Erbgang und variabler Expressivität. Die Alopecia kombiniert sich hier sowohl mit der einfach dominanten Form als auch mit der polymeren Form der Keratodermie.

Résumé

La famille décrite dans ce travail présente une alopécie congénitale, transmise selon le mode dominant incomplet avec expressivité variable. Elle est en outre associée à deux types différents de kératose palmoplantaire (type Unna-Thost et type Brünauer-Fuhs) qui semblent avoir un caractère dominant simple et polymérique.

REFERENCES

1. *Touraine, A.:* L'hérédité en médecine (a. page 531; b. page 115; c. page 443). (Masson, Paris 1955.)
2. *Templeton, H.:* Arch. Derm. Syph., Chicago *49:* 318 (1949).
3. *Lundbäck, H.:* Acta derm.-vener. *25:* 189 (1944).
4. *Sobajima, W.:* Jap. J. Derm. Urol., *27:* 28 (1927). Ref. Zbl. Haut-Geschlkr. *27:* 277 (1928).
5. *Cockayne, E.:* Inherited abnormalities of the skin. (London 1933.)
6. *Schultz, .:* Verh. Riga Ges. dtsch. Ärzte 1891; cit. by *Jadassohn, J.* in Handbuch f. Haut- u. Geschlechtskrankheiten (Springer, Berlin 1932, Vol. *XIII 1*, p. 191.
7. *Tappeiner, J.:* Zbl. Haut-Geschlkr. *57:* 644 (1938).
8. *Siemens, W.:* Arch. Derm. Syph., Berlin, *157:* 392 (1929).
9. *Hudelo, L. and Rabut, R.:* Zbl. Haut-Geschlkr. *27:* 782 (1928).
10. *Schmidt, P. W.:* Zbl. Haut-Geschlkr. *54:* 297 (1937).

Author's address: D. Stevanović, M. D. M. Sc-Camb., 46a, Neman jina St, *Beograd* (Yugoslavia).

Ziegelmayer, G. und Liebrich, K.: Acta genet. *9*: 135—148 (1959)

Aus dem Institut für Anthropologie und Humangenetik der Universität München
(Direktor: Prof. Dr. Dr. K. Saller)

STATISTISCHE UNTERSUCHUNGEN ZUR AUGENFARBENVERTEILUNG IM SÜDBAYERISCHEN RAUM UNTER ANWENDUNG DER NACH ANSCOMBE MODIFIZIERTEN WINKELTRANSFORMATION

Von G. ZIEGELMAYER und K. LIEBRICH

In einem Bericht über die regionale Verteilung der Blutgruppen (AB0-system) und der Augenfarben in Oberbayern und Schwaben im Rahmen der Tagung der Deutschen Gesellschaft für Anthropologie in Kiel 1958 *(Schwarzfischer, Ziegelmayer)* brachten wir die ersten Ergebnisse über unsere Untersuchungen zur Anthropologie Bayerns. Es hat sich gezeigt, daß die regionale Verteilung der Irisfarben, ebenso wie die der Blutgruppen im bayerischen Raum unterschiedlich ist, daß sich die Gebiete mit unterschiedlicher Verteilung der einzelnen Merkmale deutlich voneinander abgrenzen lassen und daß Beziehungen zwischen der regionalen Verteilung der Blutgruppen und derjenigen der Augenfarben zu bestehen scheinen.

Als einfaches und wirkungsvolles Verfahren für die statistische Auswertung der beobachteten relativen Häufigkeiten haben wir bei den Einzeluntersuchungen zur Verteilung der Augenfarben zunächst das Chi-Quadrat-Verfahren angewandt. Um jedoch prüfen zu können, inwieweit sich die gefundenen Zusammenhänge in der Verteilung der Augenfarben und der Blutgruppen statistisch objektivieren lassen und außerdem die Basis dafür zu schaffen, noch andere für die Anthropologie interessante Merkmale in diese Untersuchung einbeziehen zu können, war es erforderlich, den bisherigen Ergebnissen eine andere statistische Form zu geben. Wir mußten uns nach einer Methode umsehen, die eine Mehrmerkmalsanalyse zuläßt bei gleichzeitiger Berücksichtigung von Alternativmerkmalen und normal

verteilten, kontinuierlichen Merkmalen. *R. A. Fisher* hat gezeigt, daß man durch die sogenannte *Winkeltransformation* (arc-sin-Transformation) in der Lage ist, die Grundlagen für eine solche Analyse zu schaffen. *Anscombe* hat diese Methode in der Weise modifiziert, daß sie auch bei kleineren Stichprobenumfängen anwendbar wird. Da dieser *Anscombe*schen Methode zur Beantwortung anthropologischer Fragestellungen unserer Meinung nach eine wesentliche Bedeutung zukommen kann, soll in den folgenden Ausführungen am Beispiel der Augenfarbenverteilung im südbayerischen Raum diese Methodik und ihre Anwendung erörtert werden.

1. Problemstellung und statistisches Modell

Es soll untersucht werden, ob in der Verteilung der Augenfarben im südbayerischen Raum regionale Unterschiede bestehen. Zur Bearbeitung dieser allgemeinen Fragestellung war es notwendig, sie zu konkretisieren und gewisse vereinfachende Annahmen einzuführen.

Der Kennzeichnung der Augenfarben diente eine Alternativ-Klassifizierung und zwar wurde eine Augenfarbe als *hell* (H) bezeichnet, wenn sie nach der Farbtafel von *Martin-Schultz* einer der Farben 1a – 6 entsprach, als *dunkel* (D), wenn sie mit einer der Farben 7–16 übereinstimmte. Diese willkürliche Aufteilung war notwendig, um eine zu große Aufsplitterung unseres Stichprobenmaterials zu vermeiden.

Folgendes wahrscheinlichkeitstheoretisches Modell wurde der statistischen Untersuchung zugrunde gelegt. P sei eine eindeutig definierte Population. Die zufällige Entnahme eines Probanden aus dieser Population und die Bestimmung seiner Zugehörigkeit zu einer der beiden Augenfarben-Klassen (H oder D) wird als ein wahrscheinlichkeitstheoretisches Experiment E mit den beiden möglichen Ergebnissen H und D aufgefaßt. Erfolgt die Entnahme zu einem bestimmten Zeitpunkt t, so ist es sinnvoll anzunehmen, daß zu diesem Zeitpunkt eine wohldefinierte Wahrscheinlichkeit p (t) dafür vorliegt, daß der entnommene Proband der Klasse H angehört, d. h. daß die Realisierung des Experimentes E (genauer E | t |) das Ergebnis H liefert. Dieses Modell entspricht der Auffassung, daß das genetische Geschehen innerhalb der Population P ein stochastischer Prozeß ist. Auf die konsequente Durchführung dieses Gedankenganges mußte allerdings verzichtet werden, da die entsprechende mathematische Theorie praktischen Anwendungen dieser Art nur schwer zugänglich ist. Das Modell mußte daher durch Einführung einer zusätzlichen Annahme vereinfacht werden. Sie lautet dahingehend, daß die Wahrscheinlichkeit p (t) von der Zeit t unabhängig ist.

Diese Annahme wird in der Genetik häufig gemacht. Dabei wird meistens so vorgegangen, daß man voraussetzt, in der Population P herrsche *Panmixie*. Hierunter wird verstanden, daß die Population abgeschlossen und unendlich ist, daß hinsichtlich der Gene, die das Merkmal bestimmen, zufällige Gattenwahl und Gleichverteilung der Kinderzahl auf die möglichen Eheformen herrsche und daß außerdem die Gene keiner Mutation unterworfen sind. Aus diesen Voraussetzungen wird dann die zeitliche Invarianz der Wahrscheinlichkeit p gefolgert (siehe die ausführliche Diskussion für den Spezialfall des AB0-Blutgruppensystems bei *Schwarzfischer*). Unserer Meinung nach ist ein solches Vorgehen sicher dann bedenklich, wenn es sich um Merkmale handelt, deren Ausprägung von einer Vielzahl von Genen bestimmt wird. Es ist in diesem Fall kaum überschaubar, inwieweit die Voraussetzungen der Panmixie innerhalb der Population P als erfüllt angesehen werden können. Wir hielten es in unserem Falle für besser, die Annahme bezüglich der zeitlichen Invarianz der Wahrscheinlichkeit p so zu interpretieren, daß in den betrachteten Populationen diese zeitliche Variabilität von p zwar nicht ausgeschlossen ist (was die Voraussetzung der Panmixie tut), daß sie aber für so klein angesehen werden kann, daß man sie bei den vorliegenden Untersuchungen mit ihrer groben Merkmalsklassifizierung nicht zu berücksichtigen braucht.

Die vollständige Kennzeichnung des Experimentes E erfordert es, die zugrunde gelegte Population P genau zu definieren. Unter alleiniger Berücksichtigung geographischer Gesichtspunkte definierten wir die einzelnen Populationen P als die Gesamtheit der Einwohner eines bestimmten Landkreises. Es war auch hier notwendig, eine vereinfachende Annahme einzuführen, nämlich die, daß die einzelnen Landkreise in sich homogen seien. Dies soll besagen, daß es nicht möglich sein darf, einen Landkreis L bzw. die zugehörige Population P so in zwei Teilpopulationen P_1 und P_2 aufzuteilen, daß die Wahrscheinlichkeit für das Auftreten etwa der hellen Augenfarbe (H) in P_1 von derjenigen in P_2 verschieden ist. Diese Annahme entspricht genetisch der Voraussetzung, daß innerhalb eines Landkreises keine Isolate bestehen dürfen.

Es soll nicht verschwiegen werden, daß diese Annahme nur sehr bedingt zutrifft. Beispielsweise ist es nach unseren inzwischen bei anderen Untersuchungen gewonnenen Erkenntnissen unumgänglich notwendig, die Landkreise Traunstein und Pfaffenhofen noch weiter zu gliedern. Für eine erste Untersuchung halten wir unser Vorgehen jedoch für gerechtfertigt.

Schließlich wurde noch angenommen, daß die einzelnen Populationen P unendlich seien, so daß also die Stichproben als Stichproben aus einem unendlichen Kollektiv aufgefaßt wurden.

Den Stichproben lagen die ihm Rahmen erbbiologischer Gutachten an unserem Institut erhobenen Befunde zugrunde. Es handelt sich also um ausgesprochene *Gelegenheitsstichproben* mit allen Mängeln, die diesem Erhebungsverfahren anhaften. Es gibt jedoch kaum eine andere Möglichkeit ohne allzugroßen finanziellen Aufwand zu Stichproben aus einem so großräumigen Gebiet zu gelangen. Trotz mancher Bedenken gegen unser

Material hielten wir daher seine Auswertung im Rahmen einer ersten, orientierenden Untersuchung für vertretbar.

2. Methoden der statistischen Auswertung

Die Erhebung einer Stichprobe aus untereinander (bezüglich des betrachteten Merkmals) unabhängigen Individuen der Population P ist eine N-fache Realisation des Experimentes E, wenn N der Umfang der Stichprobe ist. Dies kann auch als Realisation eines einzigen Experimentes $E^{(N)}$ aufgefaßt werden, nämlich desjenigen, das in der N-fachen unabhängigen Wiederholung von E besteht.

Die Ergebnis-Menge des Experimentes $E^{(N)}$ besteht aus der Gesamtheit der ganzen Zahlen x mit $0 \leq x \leq N$, wobei das Ergebnis x bei einer Realisation von $E^{(N)}$ als eingetreten gilt, wenn x unter den N-Realisationen von E, aus denen die Realisation von $E^{(N)}$ besteht, das Ergebnis H geliefert haben. Die auf dieser Ergebnismenge definierte reelle Funktion

$$\xi = \xi(x) = x \qquad 0 \leq x \leq N$$

ist dann eine Zufallsvariable mit einer *Bernoulli*-Verteilung $B_N(x;p)$ der Parameter p und N. Erwartungswert und Varianz von ξ sind bekanntlich

$$E(\xi) = Np$$
$$V(\xi) = Npq. \qquad (q = 1 - p)$$

Die normierte Zufallsvariable

$$\pi(N) = \frac{1}{N}\xi = \frac{x}{N},$$

die sogenannte relative Häufigkeit, hat dann den Erwartungswert und die Varianz

$$E(\pi) = p$$
$$V(\pi) = \frac{pq}{N}.$$

Es ist π eine konsistente, erwartungstreue (unbiassed) und effiziente *Schätzfunktion* für den Parameter p (d. h. für die Wahrscheinlichkeit p). Der Wert $\hat{p}$, den π bei einer Realisation von $E^{(N)}$ annimmt, ist ein *Schätzwert* für den Parameter p.

Für große Werte von N ist π annähernd normal verteilt mit dem Erwartungswert $m = p$ und der Varianz $\sigma^2 = \frac{pq}{N}$.

Außerordentlich erschwerend für viele statistische Untersuchungen ist der Umstand, daß die Varianz σ^2 nicht von dem Erwartungswert m unabhängig ist. Dies macht sich besonders bemerkbar, wenn simultan mit dem Alternativmerkmal noch kontinuierliche, normal verteilte Merkmale in

Betracht gezogen werden. Die einer Stichprobe solcher normal verteilter Merkmale zugeordneten Schätzfunktionen für den Erwartungswert und die Varianz der Normalverteilung – arithmetisches Mittel und Varianz der Stichprobenwerte – sind dann voneinander unabhängig. (*Geary* hat gezeigt, daß diese Eigenschaft ausschließlich Stichproben aus einer Normalverteilung zukommt.) Alle statistischen Methoden, die für Stichproben aus einer Normalverteilung entwickelt wurden – *Student*-Test, Varianzanalyse, Verallgemeinerter Abstand D^2, Diskriminanzanalyse u. a. – setzen diese Tatsache voraus. Eine direkte Mehrmerkmalsanalyse (Mulivariate Analysis) eines Alternativmerkmals gemeinsam mit normalverteilten, kontinuierlichen Merkmalen nach einer dieser Methoden ist daher auch bei großen Stichprobenumfängen nicht möglich.

R. A. Fisher hat unseres Wissens erstmals einen Weg angegeben, durch den diese Schwierigkeiten überwunden werden können. Es wird hierzu die Zufallsvariable π so in eine neue Zufallsvariable ψ transformiert, daß ψ eine von dem Erwartungswert E (ψ) unabhängige Varianz V (ψ) besitzt. *Fisher* hat gezeigt, daß die sogenannte *Winkeltransformation* oder auch «arc sin-Transformation» dies leistet. Diese Eigenschaft gilt allerdings nur asymptotisch, d. h. mit ausreichender Näherung nur für große Stichprobenumfänge. Für kleine Stichprobenumfänge dagegen hängt V (ψ) in schwachem Ausmaß von E (ψ) ab.

Anscombe (siehe auch *Rao*) konnte zeigen, daß man durch eine geringfügige Modifikation der üblichen Winkeltransformation zu einer Zufallsvariablen α gelangen kann, für welche die Unabhängigkeit der Varianz V (α) vom Erwartungswert E (α) praktisch bereits bei sehr kleinen Stichprobenumfängen als gegeben angesehen werden darf. Da unsere Stichprobenumfänge teilweise klein sind, haben wir unseren Untersuchungen die *Anscombe*sche Transformation zugrunde gelegt.

Nach *Anscombe* wird zunächst anstelle der Zufallsvariablen π die neue Zufallsvariable

$$\varrho = \frac{x + 0{\cdot}375}{N + 0{\cdot}750}$$

eingeführt, deren Erwartungswert bzw. Varianz

$$E(\varrho) = \frac{Np + 0{\cdot}375}{N + 0.750} \qquad \text{bzw.} \qquad V(\varrho) = \frac{Npq}{(N + 0{\cdot}750)^2}$$

sind. ϱ wird dann der arc sin-Transformation unterworfen

$$\alpha = \text{arc sin } \sqrt{\varrho},\ 0° \leq \alpha < 90°, \text{ bzw. } \varrho = \sin^2\alpha.$$

Für die transformierte Zufallsvariable ist dann

$$E(\alpha) = \arcsin \sqrt{E(\varrho)} \text{ und } V(\alpha) = \frac{16.200}{(2N+1)\,\pi^2},$$

wobei außerdem die Verteilung von α asymptotisch normal mit den angegebenen Parametern ist. Nach einem in *Rao* angegebenen Satz ist α außerdem eine konsistente, erwartungstreue und effiziente Schätzfunktion für $\arcsin \sqrt{E(\varrho)}$, d. h. der aus einer Stichprobe ermittelte Wert $\hat{\alpha}$ ist ein Schätzwert für diese Größe. Es wird dann

$$p' = p'(\alpha) = \frac{(N + 0{\cdot}750)\sin^2 \alpha - 0{\cdot}375}{N}$$

eine erwartungstreue Schätzfunktion für p, die konsistent und effizient ist, da $p'(\alpha)$ die Varianz

$$V(p') = \frac{pq}{N}$$

besitzt. Mit der nach *Anscombe* modifizierten Winkeltransformation ist somit kein Verlust an Information verbunden.

Zur praktischen Bestimmung von α wurde zunächst aus jeder Stichprobe der beobachtete Wert $\hat{\varrho}$ ermittelt und anschliessend $\hat{\alpha}$ mittels einer Tabelle der arc sin-Transformation unmittelbar bestimmt (siehe *Fisher-Yates*, Tab. X). Wenn nötig, wurde hierbei linear interpoliert.

Zur Prüfung der Homogenität der Stichproben gingen wir folgendermaßen vor. Es seien

$$\hat{\alpha}_1, \hat{\alpha}_2, \ldots, \hat{\alpha}_k$$

die zu k unabhängigen Stichproben der Umfänge

$$N_1, N_2, \ldots, N_k$$

gehörigen Schätzwerte für $E(\alpha_i)$. Wir prüften dann die Hypothese

$$E(\alpha_1) = E(\alpha_2) = \ldots = E(\alpha_k).$$

Ist $E(\alpha)$ der gemeinsame Wert der $E(\alpha_i)$ so ist $\hat{\alpha}_i$ ein Schätzwert vom Gewicht $(2N_i + 1)$ für $E(\alpha)$, da die Varianz von α_i umgekehrt proportional zu $(2N_i + 1)$ ist. Es ist dann

$$\hat{\alpha} = \frac{1}{G} \sum_i (2N_i + 1)\,\hat{\alpha}_i$$

ein Schätzwert für $E(\alpha)$, wobei

$$G = 2(N_1 + N_2 + \ldots + N_k) + k = 2N + k$$

gesetzt wurde. Setzt man weiter

$$(2N_i + 1)\,V(\alpha_i) = (2N + 1)\,V(\alpha) = \sigma^2,$$

also

$$V(a_i) = \frac{\sigma^2}{(2N_i + 1)}, \qquad i = 1, 2, \ldots, k,$$

und

$$S = \sum_i (2N_i + 1)(a_i - \bar{a}),$$

so ist die Prüfgröße

$$\chi^2 = \frac{S}{\sigma^2} = \frac{S}{(2N + 1)\, V(a)} = \frac{\pi^2 S}{16.200}$$

verteilt wie Chi-Quadrat von $(k-1)$ Freiheitsgraden *(Rao)*. Die Nullhypothese $E(a_i) = E(a)$, $i = 1, 2, \ldots, k$, war dann zu verwerfen, wenn die Überschreitungswahrscheinlichkeit der aus den Stichproben errechneten Prüfgrösse $\chi^2_{emp.}$ kleiner als 5% war.

3. Ergebnisse der statistischen Auswertung

Untersucht wurden insgesamt 4668 Probanden aus 68 Landkreisen der Regierungsbezirke *Schwaben*, *Oberbayern* und *Niederbayern*. In der Tabelle 1 ist für jeden Landkreis der Stichprobenumfang (N), die beobachtete absolute Häufigkeit der helläugigen (H) bzw. der dunkeläugigen (D) Probanden und die prozentuale Häufigkeit $100\,p\%$ der helläugigen Probanden angegeben. Außerdem enthält die Tabelle für jeden Landkreis die Ergebnisse der nach *Anscombe* modifizierten Winkeltransformation, nämlich die beobachteten Werte $\hat{\varphi}$ und $\hat{a}$ der Zufallsvariablen φ, a.

Wir prüften zunächst, ob die insgesamt 68 Stichproben, die zu den einzelnen Landkreisen gehören, Stichproben aus der gleichen übergeordneten Population sind. Dabei wandten wir drei verschiedene Verfahren an, nämlich

1. Homogenitätsprüfung nach dem Chi-Quadrat-Verfahren (2×68-Tafel);
2. Homogenitätsprüfung unter Anwendung der gewöhnlichen Winkeltransformation;
3. Homogenitätsprüfung unter Anwendung der modifizierten Winkeltransformation.

Bei jeder dieser Prüfungen ergibt sich eine Prüfgröße $\chi^2_{emp.}$, die bei Gültigkeit der Prüfhypothese wie Chi-Quadrat von $n = 67$ Freiheitsgraden verteilt ist. Im einzelnen erhielten wir nachstehende Werte:

Tabelle 1

Lfd. Nr.	Landkreis	N	H	D	$100\,\hat{p}$ %	$100\,\hat{\varrho}$ %	$\hat{a}^\circ$
1	Aichach	29	21	8	72·41	71·85	57·95
2	Altötting	93	62	31	66·67	66·53	54·65
3	Augsburg	243	146	97	60·08	60·05	50·80
4	Bad-Tölz	44	25	19	56·82	56·70	48·85
5	Bogen	26	18	8	69·23	68·69	55·98
6	Bad-Aibling	25	20	5	80,00	79·13	62·82
7	Berchtesgaden	35	19	16	54·29	54·19	47·40
8	Dachau	31	12	19	38·71	38·98	38·64
9	Deggendorf	77	47	30	61·04	60·93	51·31
10	Dillingen	42	25	17	59·52	59·36	50·39
11	Dingolfing	30	14	16	46·67	46·75	43·13
12	Donauwörth	12	7	5	58·33	57·84	49·51
13	Ebersberg	45	29	16	64·44	64·21	53·26
14	Eggenfelden	66	49	17	74·24	73·97	59·32
15	Erding	81	48	33	59·26	59·17	50·28
16	Freising	33	19	14	57·57	57·41	49·25
17	Friedberg	31	16	15	51·61	51·57	45·90
18	Fürstenfeldbruck	81	52	29	64·20	64·07	53·17
19	Füssen	38	20	18	52·63	52·58	46·48
20	Garmisch-Partenkirchen	68	43	25	63·24	63·09	52·59
21	Grafenau	46	29	17	63·04	62·83	52·44
22	Griesbach	123	75	48	60·98	60·91	51·30
23	Günzburg	47	32	15	68·09	67·80	55·43
24	Illertissen	55	39	16	70·91	70·63	57·18
25	Ingolstadt	82	50	32	60·98	60·88	51·28
26	Kaufbeuren	47	30	17	63·83	63·61	52·90
27	Kelheim	89	53	36	59·55	59·47	50·46
28	Kempten	113	67	46	59·29	59·23	50·31
29	Krumbach	40	25	15	62·50	62·27	52·10
30	Landau	38	27	11	71·05	70·65	57·20
31	Landsberg	42	28	14	66·67	66·37	54·55
32	Landshut	73	42	31	57·53	57·46	49·28
33	Laufen	44	28	16	63·64	63·41	52·78
34	Lindau	85	53	32	62·35	62·24	52·08
35	Mainburg	21	16	5	76·19	75·29	60·19
36	Mallersdorf	70	40	30	57·14	57·07	49·06
37	Marktoberdorf	13	7	6	53·84	53·64	47·08
38	Memmingen	44	26	18	59·14	58·94	50·14
39	Miesbach	51	33	18	64·71	64·49	53·42
40	Mindelheim	41	22	19	53·66	53·59	47·05
41	Mühldorf	65	46	19	70·77	70·53	57·12
42	München	676	396	280	58·58	58·57	49·93
43	Neu-Ulm	23	12	11	52·17	52·10	46·20

Tabelle 1 (Fortsetzung)

Lfd. Nr.	Landkreis	N	H	D	100 $\hat{p}$ %	100 $\hat{q}$ %	$\hat{\alpha}$ °
44	Neuburg a.D.	53	39	14	73·58	73·26	58·86
45	Nördlingen	29	19	10	65·52	65·13	53·81
46	Passau	153	96	57	62·74	62·68	52·35
47	Pfaffenhofen	40	25	15	62·50	62·27	52·20
48	Pfarrkirchen	74	49	25	66·22	66·05	54·36
49	Regen	75	49	26	65·33	65·18	53·84
50	Regensburg	111	66	45	59·46	59·39	50·41
51	Rosenheim	96	61	35	63·54	63·44	52·80
52	Rottenburg	30	22	8	73·33	72·76	58·53
53	Schongau	44	29	15	65·91	65·64	54·11
54	Schrobenhausen	26	19	7	73·08	72·43	58·32
55	Schwabmünchen	71	51	20	71·83	71·60	57·80
56	Sonthofen	48	18	30	37·50	37·69	37·87
57	Starnberg	62	51	11	82·26	81·87	64·80
58	Straubing	27	18	9	66·67	66·22	54·44
59	Traunstein	85	69	16	81·18	80·90	64·08
60	Vilsbiburg	73	57	16	78·08	77·80	61·89
61	Vilshofen	77	43	34	55·84	55·79	48·33
62	Viechtach	98	71	27	72·45	72·28	58·22
63	Wasserburg	65	43	22	66·15	65·97	54·31
64	Weilheim	44	24	20	54·55	54·47	47·56
65	Wegscheid	22	14	8	63·64	63·19	52·65
66	Wertingen	16	10	6	62,50	61·94	51·90
67	Wolfstein	162	91	71	56·17	56·14	48·52
68	Wolfratshausen	129	17	12	58·62	58·40	49·83
	Gesamt	4 668	2 919	1 749	62·53	62·55	52·27

1. Chi-Quadrat-Test: $\chi^2_{emp.} = 107{\cdot}852$
2. Winkeltransformation: $\chi^2_{emp.} = 133{\cdot}667$
3. mod. Winkeltransformation: $\chi^2_{emp.} = 112{\cdot}385$

Bei n = 67 Freiheitsgraden kommt dem Wert $\chi^2 = 108{\cdot}524$ die Überschreitungswahrscheinlichkeit P = 0·1% zu. Alle drei Prüfverfahren führen somit eindeutig zum Verwerfen der Prüfhypothese; es kann also Heterogenität zwischen den Verteilungen der Augenfarben, die zu den einzelnen Landkreisen gehören, angenommen werden.

Die Größenordnungen der einzelnen Prüfgrößen erscheinen nicht uninteressant, insbesondere der Unterschied zwischen den zur gewöhnlichen, beziehungsweise zur modifizierten Winkeltransformation gehörigen Werten. Die gewöhnliche Winkeltransformation führt im Vergleich zum Chi-Quadrat-Test zu einem exessiv hohen Prüfwert, ebenso im Vergleich

zur modifizierten Winkeltransformation, und führt somit möglicherweise zu einer Überschätzung der Heterogenität. Die Verkleinerung des Prüfwertes bei Anwendung der modifizierten Winkeltransformation hat ihre Ursache darin, daß für die in einer Stichprobe beobachteten Werte $\hat{\varphi}$ beziehungsweise $\hat{a}$ der Zufallsvariablen φ und a gilt:

$$\hat{\varphi} < \hat{a} < 45^\circ \text{ falls } \hat{\varphi} < 45^\circ$$
$$\hat{\varphi} = \hat{a} = 45^\circ \text{ falls } \hat{\varphi} = 45^\circ$$
$$\hat{\varphi} > \hat{a} > 45^\circ \text{ falls } \hat{\varphi} > 45^\circ$$

Die Werte $\hat{a}$ für die einzelnen Stichproben liegen somit enger um den Zentralwert 45° des Wertebereiches als die Werte φ und weisen somit untereinander eine kleinere Varianz auf als die $\hat{\varphi}$-Werte.

Die nunmehr erkannte Heterogenität zwischen den Landkreisen rechtfertigt den Versuch, einzelne Landkreise so zu Landkreisgruppen zusammenzufassen, daß zwischen den zu einer Gruppe gehörigen Landkreisen keine Heterogenität feststellbar ist, wohl aber zwischen den Landkreisgruppen selber. Die Form, in der diese Bildung von insgesamt 11 Landkreisgruppen vorgenommen wurde, läßt sich aus der Karte ersehen. Sie wurde vornehmlich von geographischen Gesichtspunkten bestimmt. In einer späteren Arbeit, in der diese Ergebnisse mit den Ergebnissen von *Schwarzfischer* über die regionale Gliederung der AB0-Blutgruppen verglichen werden sollen, wird versucht werden, zur Bildung der Landkreisgruppen objektive Kriterien heranzuziehen.

Gegenüber den Ergebnissen unseres ersten Berichtes wurde die Einteilung in Landkreisgruppen etwas modifiziert, sie wurde im wesentlichen verfeinert. Nähere Einzelheiten ergeben sich aus der Karte und der zugehörigen Legende.

Die Tabelle 2 enthält für jede Landkreisgruppe den Stichprobenumfang (N), die beobachtete absolute Häufigkeit der helläugigen (H) und der dunkeläugigen (D) Probanden. Für jede Landkreisgruppe ist außerdem das gewichtete Mittel $\bar{a}$ der in den zugehörigen Landkreisen beobachteten $\hat{a}_i$ angegeben. $\bar{a}$ ist ein Schätzwert für den Erwartungswert E (a) der Zufallsvariablen a innerhalb der betreffenden Landkreisgruppe. Der aus $\bar{a}$ ermittelte Schätzwert $\dot{p}$ (a) für die Wahrscheinlichkeit p findet sich gleichfalls in der Tabelle. ($\dot{p}$ (a) ist nicht identisch mit der relativen Häufigkeit der helläugigen Individuen, die Abweichung ist jedoch nur unerheblich.)

Für jede Landkreisgruppe wurde einzeln geprüft, ob die in ihr vereinigten Landkreise hinsichtlich der Verteilung der Augenfarben als homogen angesehen werden können, wobei dieser Prüfung die modifizierte Winkeltransformation zugrunde gelegt wurde. Die Ergebnisse finden sich ebenfalls in der Tabelle 2 und zwar ist in der Spalte n die Zahl der Freiheitsgrade der zugehörigen Prüfverteilung (Chi-Quadrat-Verteilung) angegeben, in der Spalte $\chi^2_{emp.}$ der jeweils errechnete Prüfwert. In der Spalte P wurde ver-

Abb. 1. Geographische Lage der voneinander abgrenzbaren Landkreisgruppen mit unterschiedlicher Häufigkeit der Augenfarben. Die Zusammensetzung der Landkreisgruppen ist in der Tabelle 3 nochmals aufgeführt. Die Häufigkeit der hellen Augenfarben (Farbe 1 a – 6 nach der Vergleichstafel von *Martin-Schultz*) in diesen Landkreisgruppen ergibt sich aus der Tabelle 2.

merkt, welche Überschreitungswahrscheinlichkeit dem Prüfwert $\chi^2_{emp.}$ *mindestens* zukommt. Es zeigt sich, daß für keine der Landkreisgruppen die Hypothese verworfen werden muß, die in ihr vereinigten Landkreise seien hinsichtlich der in ihnen vorliegenden Verteilung der Augenfarben homogen.

Dieser Test diente der Kontrolle der von uns auf Grund der Stichprobenergebnisse getroffenen Einteilung in Landkreisgruppen. Die auf-

Tabelle 2

Landkreisgruppe	N	H	D	$\hat{p}(\alpha)$	$\hat{\alpha}$	n	$\chi^2_{emp.}$	P
Gruppe 1	353	213	140	60·25	50·90	4	0·1368	99%
Gruppe 2	173	122	51	70·36	56·96	2	0·2002	99%
Gruppe 3	249	142	107	56·95	48·98	4	0·8907	95%
Gruppe 4	282	182	100	64·39	53·34	4	0·1690	99%
Gruppe 5	159	117	42	73·15	57·82	4	0·0857	99%
Gruppe 6	348	212	136	60·83	51·24	4	0·9221	90%
Gruppe 7	1 142	653	489	57·14	49·10	10	1·4320	99%
Gruppe 8	257	166	91	64·47	53·39	3	0·1095	99%
Gruppe 9	242	179	63	73·81	59·17	3	1·1829	80%
Gruppe 10	167	111	56	66·39	54·52	1	0·0042	90%
Gruppe 11	496	310	186	62·41	52·18	5	0·4568	99%

tretenden hohen P-Werte dürfen somit nicht überbewertet werden, da die Einteilung mit dem Ziel getroffen wurde, geographisch zusammenhängende Gebiete (Landkreisgruppen) mit maximaler Homogenität voneinander abzugrenzen.

Abschließend wurde noch geprüft, ob die Landkreisgruppen untereinander homogen sind. Es ergab sich hierbei, wiederum bei Anwendung der modifizierten Winkeltransformation, der Prüfwert

$$\chi^2_{emp.} = 47{\cdot}005,$$

dem in der Chi-Quadrat-Verteilung von n = 10 Freiheitsgraden eine Überschreitungswahrscheinlichkeit zukommt, die wesentlich kleiner ist als 0·1%. Es darf daher als statistisch gesichert angesehen werden, daß zwischen den Landkreisgruppen, hinsichtlich der in ihnen bestehenden Verteilungen der Augenfarben, eine starke Heterogenität vorliegt.

4. Zusammenfassung

An einem Gesamtmaterial von 4668 Befunden, welches sich aus Stichproben aus den einzelnen Landkreisen zusammensetzt, konnte festgestellt werden, daß im bayerischen Raum südlich der Donau regionale Unterschiede in der Verteilung der hellen und dunklen Augenfarben vorliegen (siehe Tabelle 1). Mit Hilfe der von *Anscombe* modifizierten Winkeltransformation konnten 11 Landkreisgruppen voneinander abgegrenzt werden, zwischen denen statistisch gesicherte Unterschiede hinsichtlich der Verteilung der Augenfarben bestehen (siehe Tabelle 2). Die 1958 von *Ziegel-*

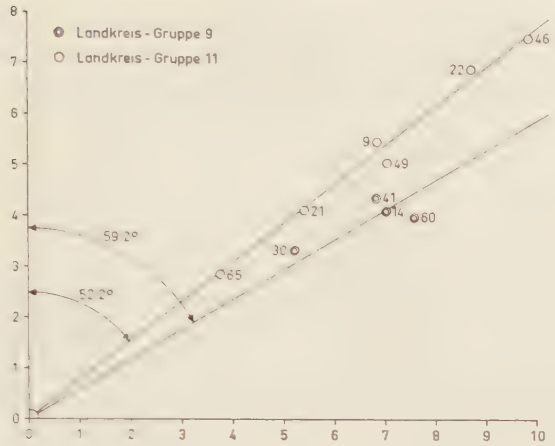


Abb. 2. Gewöhnliche Winkeltransformation: Jeder Punkt entspricht der beobachteten Häufigkeit in einem Landkreis. Der Winkel, den die Verbindungsgerade eines Punktes mit dem Nullpunkt mit der Ordinate bildet, ist die transformierte Zufallsvariable φ. Je größer φ, um so größer ist der Prozentsatz der Helläugigen. Der Abstand eines Punktes vom Nullpunkt ist $\sqrt{N}$; N = Umfang der Stichproben. Die Gerade entspricht dem Mittelwert $\hat{a}$ innerhalb der Landkreisgruppe.

Die Prozentwerte für die hellen Augenfarben in den einzelnen Landkreisen der beiden Landkreisgruppen 9 und 11 sind in der folgenden Tabelle nochmals zusammengefaßt.

	Lfd. Nr.	Landkreis	helle Augenfarbe		Lfd. Nr.	Landkreis	helle Augenfarbe
Gruppe 9	14	Eggenfelden	74,24%	Gruppe 11	9	Deggendorf	61,04%
	30	Landau	71,05%		21	Grafenau	63,04%
	41	Mühldorf	70,77%		22	Griesbach	60,98%
	60	Vilsbiburg	78,08%		46	Passau	62,74%
					49	Regen	65,33%
					65	Wegscheid	63,64%
		Mittel	73,81%			Mittel	62,41%

mayer zur gleichen Frage gebrachten Untersuchungsergebnisse konnten auf Grund der jetzt vorliegenden statistischen Bearbeitung erweitert werden. Einzelne größere Gebiete mußten unterteilt werden, einige Landkreise konnten nicht einer Landkreisgruppe zugeordnet werden, zum Teil weil sie bezüglich der Merkmalsverteilung auf Grund ihrer randständigen Lage wahrscheinlich zu Nachbargebieten gehören, die in die Untersuchung nicht einbezogen wurden. Es zeigt sich für die in der Abbildung dargestellten Landkreisgruppen mit unterschiedlicher Augenfarbenhäufigkeit eine auffallende Parallelität zu den Landkreisgruppen, die sich nach den

Tabelle 3

Zusammenstellung über die Zusammensetzung der Landkreisgruppen

Gruppe 1
- Augsburg
- Dillingen
- Donauwörth
- Krumbach
- Wertingen

Gruppe 2
- Günzburg
- Illertissen
- Schwabmünchen

Gruppe 3
- Füssen
- Kempten
- Marktoberdorf
- Memmingen
- Mindelheim

Gruppe 4
- Fürstenfeldbruck
- Garmisch-Partenkirchen
- Kaufbeuren
- Landsberg
- Schongau

Gruppe 5
- Aichach
- Mainburg
- Neuburg a. D.
- Rottenburg
- Schrobenhausen

Gruppe 6
- Bogen
- Ingolstadt
- Kelheim
- Pfaffenhofen
- Regensburg

Gruppe 7
- Bad Tölz
- Dachau
- Dingolfing
- Erding
- Freising
- Friedberg
- Landshut
- Mallersdorf
- München
- Weilheim
- Wolfratshausen

Gruppe 8
- Ebersberg
- Miesbach
- Rosenheim
- Wasserburg

Gruppe 9
- Eggenfelden
- Landau
- Mühldorf
- Vilsbiburg

Gruppe 10
- Altötting
- Pfarrkirchen

Gruppe 11
- Deggendorf
- Grafenau
- Griesbach
- Passau
- Regen
- Wegscheid

ausgeschiedene Landkreise
- Bad Aibling
- Berchtesgaden
- Laufen
- Lindau
- Neu-Ulm
- Nördlingen
- Sonthofen
- Starnberg
- Straubing
- Traunstein
- Vilshofen
- Viechtach
- Wolfstein

Untersuchungen *Schwarzfischers* bezüglich der Verteilung der Blutgruppen (AB0-System) deutlich voneinander unterscheiden. Die Landkreise, die sich hinsichtlich der Blutgruppen nicht einer größeren Gruppe ihrer Umgebung zuordnen ließen, nehmen auch in der Verteilung der Augenfarben eine Sonderstellung ein (u. a. die Landkreise *Starnberg* und *Bad Aibling* und *Vilshofen*). In einer späteren Arbeit, in der versucht werden soll, zu objektiven Kriterien für die Bildung der Landkreisgruppen zu gelangen, werden

unsere Ergebnisse noch eingehend mit denen von *Schwarzfischer* verglichen. Die Bearbeitung des Materials mit Hilfe der Winkeltransformation bietet hierzu eine gute Basis.

Summary

From a total material (comprising 4668 individuals), composed of samples taken in the various districts (Landkreise), it was ascertained that regional differences in the distribution of light and dark eyes colors occur in the Bavarian area south of the Danube (see Table 1). With the help of *Anscombe*'s modified angle transformation it was possible to distinguish 11 district groups among which statistically substantiated differences exist in respect to eye color (see Table 2). It was also possible to extend the research results provided by *Ziegelmayer* in 1958 regarding the same matter by use of the statistical compilation presented here. Various larger areas had to be subdivided and some districts on the border could not be ranged with a district group because, in respect to the distribution of characteristics, they probably belong to neighboring areas which were not included in the examination. A striking parallelism is apparent between the district groups represented in the illustration with divergent eye-color frequencies and those district groups which differ from one another on the basis of *Schwarzfischer*'s investigations regarding the distribution of blood types (AB0). The districts which cannot be ranged with a larger group in their vicinity in respect to blood types also occupy an exceptional position in the distribution of eye colors (among others the Starnberg, Bad Aibling, and Vilshofen districts). In a later work in which the attempt will be made to reach objective criteria for the composition of the district groups, our results will be compared in detail with those of *Schwarzfischer*.

The treatment of the material with the help of the angle transformation offers a good basis for this.

Résumé

A partir d'un matériel d'ensemble, portant sur 4668 cas examinés, sélectionnés par échantillonnage dans différents districts ruraux. il a pu être établi l'existence, sur le territoire de la Bavière au sud du Danube, des écarts, d'une région à l'autre, dans la répartition des couleurs claires et foncées des yeux (voir table 1). A l'aide de la transformation angulaire, modifiée par *Anscombe*, on a pu délimiter 11 groupes de districts ruraux, présentant entre eux des écarts statistiquement étayés, en ce qui concerne la

répartition des couleurs des yeux (voir table 2). Les résultats des recherches consacrées à cette question – et qui ont été énoucés par *Ziegelmayer* en 1958 – ont pu être élargis par l'évaluation des statistiques présentement disponibles. Quelques-unes des régions plus vastes ont dû être subdivisées, pour partie parce que, relativement à la répartition des indices, elles se rapprochent, du fait de leurs situations limitrophes, plutôt des régions avoisinantes, qui, elles, n'ont pas été englobées dans l'enquête. Concernant les groupes de districts ruraux à fréquence différente de coloration des yeux, représentés sur la figure, il s'ensuit un surprenant parralélisme d'avec ceux des groupes de districts ruraux qui, d'après les recherches de *Schwarzfischer*, se distinguent nettement les uns des autres par la répartition des groupes sanguins (AB0). Ceux des districts ruraux, qui en fonction de leurs groupes sanguins n'ont pu être associés à aucun des groupes plus importants de leur ambiance, tiennent aussi un rang à part dans la répartition des couleurs oculaires (dont les districts Starnberg, Bad Aibling et Vilshofen). Dans une étude ultérieure, où il sera question d'aboutir à des critères objectifs de la formation des groupes de districts ruraux, nous mettrons nos résultats plus largement en parallèle avec ceux acquis par *Schwarzfischer*. La valorisation du matériel, à l'aide de la méthode de transformation angulaire, constitue, à cet égard, une bonne base de départ.

LITERATUR

Anscombe, F.J.: The transformation of poisson, binominal and negativ binominal data. Biometrika *35:* 246 (1948).

Fisher, R.A.: On the dominance ratio. Proc. roy. Soc. Edinb. B. *42:* 321 (1922).

Fisher, R.A.: The distribution of gene ratios for rare mutations. Proc. roy. Soc. Edinb. B. *50:* 205 (1930).

Fisher, R.A. and F.Yates: Statistical tables for biological, agricultural and medical rese arch, 5th ed. (Oliver and Boyd, Edinburgh/London 1957).

Geary, R.G.: Distribution of student's ratio for non-normal samples. J. roy. stat. Soc., Suppl. *3* (1936).

RAO, C.R.: Advanced statistical methods in biometric research. (John Wiley and Sons, Inc., New York/London 1952.)

Schwarzfischer, F.: Die regionalen Unterschiede der Blutgruppenfrequenz in Schwaben und Oberbayern. Tagung der Deutschen Gesellschaft für Anthropologie, Kiel 1958. Sonderheft Homo *1959.*

Ziegelmayer, G.: Regionale Augenfarbenverteilungen in Oberbayern, Niederbayern und Schwaben. Tagung der Deutschen Gesellschaft für Anthropologie, Kiel 1958. Sonderheft Homo *1959.*

Adresse der Autoren: Priv.-Doz. Dr. G. Ziegelmayer und K. Liebrich, Institut für Anthropologie und Humangenetik der Universität München, Richard-Wagner-Straße 10/1, *München 2* (Deutschland.)

Mäkelä, O.; Eriksson, A. W. and Lehtovaara, R.: Acta genet. *9*: 149—166 (1959)

From the Department of Serology and Bacteriology, University of Helsinki

ON THE INHERITANCE OF THE HAPTOGLOBIN SERUM GROUPS[1]

By O. MÄKELÄ, A. W. ERIKSSON and RAIMO LEHTOVAARA

In 1955 *Smithies* (12, 13), using a new starch gel electrophoretic technique, succeeded in discerning three different patterns of hemoglobin-binding proteins in the sera of different people. He identified these proteins with *Jayle*'s (10) haptoglobin (15).

Smithies and Walker (14) advanced a theory of the inheritance of haptoglobins. According to this theory the serum groups are determined by two autosomal genes with incomplete dominance. Originally the three groups were named I, IIA and IIB. As the identity of the corresponding proteins with haptoglobin seems established, *Smithies and Walker* (14) now propose the names Hp 1-1, Hp 2-1 and Hp 2–2 for the phenotypes and Hp^1 and Hp^2 for the genes.

Galatius-Jensen (4, 5) and *Fleischer and Lundevall* (3) made a further study of the inheritance of the haptoglobin groups, and their results were in agreement with the original hypothesis of *Smithies and Walker*. *Galatius-Jensen* (6) has found an additional rare phenotype, which may give rise to erroneous exclusions in cases of disputed paternity. He also found that in most newborn children no hemoglobin-binding protein could be demonstrated (4). Children with this "undeveloped" type were unusual in the group aged over 4 months. *Harris et al.* (9) studied an extensive family material and discovered four cases of incompatible homozygosity between

[1] Aided by a grant from Sigrid Jusélius Foundation.

mother and child. These persons were all closely related. The authors chose to attribute the incompatibility to a "silent" gene supposedly running in the family.

Of prime importance is the question of the existence and incidence of rare additional gene(s) in different peoples when the value of haptoglobin groups to paternity studies is to be estimated. For this reason the authors carried out studies in the haptoglobin groups in Finnish people.

Technique

The technique used in this work is essentially the same as that described in detail by *Galatius-Jensen* (4). The only exceptions are as follows:

The electrodes are immersed in the bridge solution containing 0.15 mole of H_3BO_3 and 0.03 mole of NaOH per litre. The electrical contacts to the gels are made with filter paper wads (eight layers of paper) soaked in the bridge solution. A perforated wall of plastic separates the filter papers from the electrodes. Fresh bridge solution is prepared twice a week. When the same bridge solution is used on successive days, the direction of current is from A to B on the first day, B to A on the second day, and A to B on the third.

The gel is prepared by adding 14 g of hydrolysed starch to 100 ml of buffer (0.015 mole H_3BO_3 and 0.006 mole NaOH per litre).

The sera are studied after an addition of human hemoglobin to the extent of approximately 300 mg per 100 ml. All sera are examined twice. The readings are done as blind tests and independently by two persons.

The blood samples examined in this study were grouped by means of anti-A, -A_1, -B, -M, -N, -H, -C, -D, -E, -c and "anti-Gma" (11). The last six were not used for all samples.

Some persons in the family material were tested and measured for their ability to taste phenyl thiocarbamide according to the method of *Harris and Kalmus* (8). For convenience only seven different solutions were used. Ordinary tap water was used in order to exclude suggestions and simulations. The solution numbers of P.T.C. represent serial dilutions by ¼ of solution no. 1 containing 1.3 g. P.T.C. (B.D.H.) per litre. The boundary between tasters and non-tasters lies between solutions 2 and 3.

Material

The material consists of four groups of persons: 1) unrelated healthy Finnish adults, 2) families consisting of the parents and at least one child, 3) mothers and their child, 4) monozygous and dizygous twins. Nearly all of the persons studied were over six months old.

In the calculations of gene frequencies one twin of each twin pair (picked out at random) was included as well as all Finnish parents. A considerable part of the families was from the Åland islands, the origin of whose Swedish-speaking population is uncertain. Parents of these families were not included for these calculations.

The family material comprises 126 families with 419 children tested. There was some selection for large families. In some Åland families three generations were studied.

Altogether 223 *mothers* together with an equal number of *children* (not including the family study) were studied.

The twin material is a part of the material collected by Oy Alkoholiliike Ab and comprising Finnish male twins born between 1920 and 1929. All pairs with identical blood groups and a high concordance index ($\geq = 4.7$) in polysymptomatic similarity tests were regarded as monozygous. The limit 4.7 was fixed before the Hp typing. Of the remaining twin pairs those were considered dizygous which showed differences in blood groups.

Results

The stability of the Hp-type: The Hp-type of 42 persons was determined from two or more serum samples taken at intervals of 10 to 480 days. Only two persons in the series showed a difference in the electrophoretic pattern between different blood samples. In these two persons (who were siblings aged 10 and 12) it was not possible to determine the Hp-type because no hemoglobin-binding protein fractions could be demonstrated.

Table 1

Hp Groups of Unrelated Adults in Relation to Blood Groups

	O	A_1	A_2	B	A_1B	A_2B	M	N	MN
Hp 1–1	44	46	13	17	8	1	50	17	62
Hp 2–2	125	127	30	69	15	8	134	50	190
Hp 2–1	135	138	33	59	16	5	159	54	176
Undev.		1	1				1	1	
	304	312	77	145	39	14	341	122	428

	R_1r	R_2r	rr	R_1R_1	R_1R_2	R_0r	R'r	R"r	R_1R_z	Male	Fem.	Totals
Hp 1–1	34	11	12	19	18		3		1	98	31	129
Hp 2–2	78	44	38	51	50	6	2			279	95	374
Hp 2–1	79	30	32	58	65	5	4	4		293	92	386
Undev.		1		1						1	1	2
	191	86	82	129	133	11	9	4	1	672	219	891

Serum samples taken from these persons 4 months later showed a weak pattern of type Hp 2–2, and of the samples taken after further 12 months one was a weak Hp 2–2 and another "undeveloped" again.

Of the persons studied 142 were aged between 6 and 8 months. Two of them had an "undeveloped" pattern.

Unrelated adults: As appears from Table 1, the Hp group seems to be independent of the blood groups indicated, and of sex. For this reason the pooled figures of unrelated Finnish adults have been used for the calculation of gene frequencies. The Hp groups of these adults are recorded in Table 2. When persons with an "undeveloped" type have been omitted, the gene frequencies are:

$$Hp^1 = 0.145 + \frac{0.434}{2} = 0.362$$

$$Hp^2 = 0.421 + \frac{0.434}{2} = 0.638$$

and the expected distribution of phenotypes:

$$\begin{aligned} \text{Hp 1–1} &= 0.362^2 &&= 0.131 \\ \text{Hp 2–2} &= 0.638^2 &&= 0.407 \\ \text{Hp 2–1} &= 2 \times 0.362 \times 0.638 &&= 0.462 \\ & && \overline{1.000} \end{aligned}$$

The relationship between what is observed and what was expected is shown in Table 2.

Families: The Hp-types of the family material are recorded in Table 3. The results are in accordance with the theory of *Smithies and Walker*

Table 2

Hp Groups of 891 Unrelated Adults

Type	Number		χ^2	Per cent	
	obs.	exp.		obs.	exp.
1–1	129	116.9	1.25	14.5	13.1
2–2	374	361.4	0.53	42.1	40.7
2–1	386	410.7	1.49	43.4	46.2
Undev.	2				
Totals	891	889.0	3.27	100.0	100.0
		for 1 d.f., $0.1 > p > 0.05$			

Table 3

Haptoglobin Types of Family Material

Matings		Children						
Type	Number obs.[2])	Hp 1-1 obs.	Hp 1-1 exp.	Hp 2-1 obs.	Hp 2-1 exp	Hp 2-2 obs.	Hp 2-2 exp.	undev. [3])
Hp 1–1 × 1–1	1	1	1	–	–	–	–	
Hp 1–1 × 2–2	12	–	–	43	43	–	–	
Hp 2–2 × 2–2	22	–	–	–	–	92	92	3
Hp 1–1 × 2–1[1]	24	38	35	32	35*	–	–	
Hp 2–2 × 2–1	45	–	–	78	74	70	74**	1
Hp 2–1 × 2–1	22	18	16.25	36	32.5	11	16.25***	

* $\chi^2 = 0.52$ (for 1 d.f. $0.5>p>0.3$)
** $\chi^2 = 0.44$ (for 1 d.f. $0.7>p>0.5$)
*** $\chi^2 = 2.25$ (for 2 d.f. $0.5>p>0.3$)

[1] One child of Hp-type 1–1 has been excluded on account of illegitimacy (ABO system).
[2] Not included in the calculations of expected frequencies.
[3] Expected frequencies are not calculated because the material is not homogenous and because some families are related to each other.

Table 4

Hp-Types of 222 Mother-Child Combinations

Mother		Children			
Type	Number	Type	obs.	exp.	χ^2
Hp 1–1	27	1–1	8	9.8	0.33
		2–1	19	17.2	0.19
					0.52
					for 1 d.f. $0.5>p>0.3$
Hp 2–2	92	2–2	57	58.7	0.049
		2–1	35	33.3	0.086
					0.135
					for 1 d.f. $0.75>p>0.7$
Hp 2–1	103	1–1	17	18.5	0.12
		2–2	37	32.5	0.62
		2–1	48	51.0	0.18
		undev.	1		0.92
					for 2 d.f. $0.9>p>0.8$
Totals	222		222	221.0	
					Total $\chi^2 = 1.58$ for 4 d.f.
					$0.9>p>0.8$

cited above. There were 35 families in which both parents were homozygous; in these families only one Hp-type is theoretically possible in the children. 139 children of these families showed no exception to the hypothesis. There were 69 families with one homozygous parent, and in the 219 children of these families no cases of homozygosity incompatible with the homozygous parent were encountered. Detailed data of the family material are given in the appendix.

Mother-child combinations: Altogether 223 mother-child combinations were tested. One of the mothers had an "undeveloped" type, her child was 2–1. The distribution of the remaining 222 pairs is presented in Table 4. The child with an undeveloped pattern was not included when the expected frequencies were calculated.

In the 119 children of homozygous mothers no instance of homozygosity incompatible with the mother was met with. The difference between the observed and expected distribution of children is insignificant.

Twins: 263 pairs of twins were examined. The results are in Table 5.

Linkage: Several "crossovers" between Hp genes and blood group (ABO, MN, Rh) genes, Gm genes or genes controlling the ability to taste P.T.C. were encountered in the family material.

Discussion

Distribution of Hp-types in different peoples: Those white peoples which have been studied do not seem to differ greatly in their Hp type frequencies (Table 6), and it is rare that ahaptoglobinemia occurs in healthy adults.

Table 5

The Hp-Type of 194 Pairs of Twins

	Different Hp-types	Identical Hp-types	Total
Monozygotic pairs[1]	obs. 0 pairs exp. 0 pairs	obs. 61 pairs exp. 61 pairs	61
Dizygotic pairs[1]	obs. 69 pairs exp. 73.1 pairs	obs. 133 pairs exp. 128.9 pairs	202
	$\chi^2 = 0.36$ (for 1 d.f., $0.7 > p > 0.5$)		

[1] For explanation, see the text.

Table 6

Distribution of Hp-types in Different Peoples

		No. tested	1-1	2-1 per cent	2-2	No. Ahaptogl.
White	Danish (5)	2050	16.0	47.2	36.6	0.2
	Norwegian (3)	1000	13.2	46.2	40.6	.
	Finnish	891	14.5	43.3	42.0	0.2
	Swedish (2)	220	18.6	50.0	31.4	.
	British (1)	218	10.1	55.5	31.7	2.7
	Basque (1)	107	14.0	45.7	39.3	0.9
Negr.	Ivory Coast Liberia (16)	142	48.6	42.2	9.2	.
	Nigeria (1)	99	53.5	11.1	3.0	32.3
Mixed(?)	Amer. Negr. (7)	406	26.4	31.2	38.2	4.2

The Hp^1 gene appears to be much more common in negroes than in whites. The frequency of ahaptoglobinemia in Negro populations may be, in part at least, due to the fact that the persons examined have not all been healthy (secondary ahaptoglobinemia being caused by hemolytic diseases of the blood).

Silent alleles: The present study supports the theory that haptoglobins are controlled by two autosomal incompletely dominant alleles. The maximum total frequency of a hypothetical "silent" allele in the Finnish population can be estimated on the basis of the studied mother-child combinations. The probability of demonstrating such a (rare) allele (designated Hp^0) by apparent mother-child exclusion is approximately:

$2 \cdot Hp^1 \cdot Hp^2 \cdot Hp^0 = 2 \cdot 0.362 \cdot 0.638 \cdot Hp^0 = 0.462 \cdot Hp^0$

If the distribution of apparent mother-child exclusions due to Hp^0 is a Poisson distribution, the upper limit of their frequency based upon the 300 mother-child combinations studied (all Finnish mothers and one child of each) will be about 0.01, if a confidence limit of 95% is chosen. This corresponds to an upper limit of frequency of a hypothetical "silent" allele of about 0.02.

The frequency of erroneous exclusions of paternity based on apparent incompatible homozygosity in man and child is the same as the frequency of apparent mother-child exclusions, *i.e.*, the upper limit in Finland is about 0.01 (with the confidence limit of 95%).

The results that were obtained do not constitute palpable proof of the existence of the hypothetical "silent" allele. Notwithstanding, there is an excess of homozygotes among the 891 unrelated persons (Table 2). This excess just falls short of significance. Its existence may be accounted for e.g. by assuming that part of the apparent homozygotes are heterozygous with regard to the "silent" allele.

Persons with an "undeveloped" type: In the material there were two adults with an "undeveloped" haptoglobin type. One of them (mother) had a 2–1 child. In addition, there were five such persons aged 10 to 20, and three of them had a 2–1 parent. Two of the last three had a weak Hp 2–2 pattern in a control study 4 months later, and after further 12 months one of them was a weak 2–2, another "undeveloped" again. An "undeveloped" pattern in an apparently healthy adult thus does not seem to be due to his homozygosity with regard to the hypothetical "silent" allele Hp^0, at least not in all cases.

Difficulties arise also if an explanation of those persons' Hp-type is attempted by assigning them the genotype $Hp^1\ Hp^0$ or $Hp^2\ Hp^0$ because the parental type turned out to be the normal 2–1 or 2–2 in all the five cases where the parents were examined. The likeliest explanation appears to be that, for some unidentified secondary reason, their output of haptoglobin was low or its consumption high.

Linkage: On the basis of the above results no close linkage can be said to exist between Hp-groups and blood groups (ABO, MN, Rh), Gm-group or ability to taste P.T.C.

Summary

Hp-groups of 891 healthy unrelated adults, 126 families with 419 children, 222 mother-child combinations and 263 pairs of twins were determined. The results support the theory that Hp types are controlled by two autosomal alleles with incomplete dominance. The Finnish gene frequencies are estimated to be Hp^1 0.362 and Hp^2 0.638. There seems to be no close linkage between Hp groups and blood groups (ABO, MN, Rh), Gm-groups or ability to taste phenyltiocarbamide.

Zusammenfassung

Bei 891 gesunden nicht miteinander verwandten Erwachsenen, 126 Familien mit 419 Kindern, 222 Mutter-Kind-Kombinationen und 263 Zwillingspaaren wurden Hp-Gruppen bestimmt. Die Ergebnisse bestätigen die Theorie, daß die Haptoglobine von 2 autosomalen Allelen mit unvoll-

ständiger Dominanz kontrolliert werden. Die Genhäufigkeit in Finnland wird auf Hp^1 0,326 und Hp^2 0,638 geschätzt. Eine enge Koppelung zwischen Haptoglobinen und Blutgruppen (ABO, MN, Rh) sowie den Gm-Gruppen oder der Fähigkeit, Phenyltiocarbamide zu schmecken, scheint nicht zu bestehen.

Résumé

Les groupes Hp ont été examinés chez 891 adultes, chez 126 familles avec 419 enfants, chez 222 enfants et leurs mères et chez 263 paires de jumeaux. Les résultats permettent d'émettre l'hypothèse que les types Hp dépendent de deux allèles autosomaux avec dominance incomplète. La fréquence des gènes en Finlande est évaluée à 0,362 pour Hp^1 et 0,638 pour Hp^2. Il ne semble pas y avoir de linkage étroit entre les groupes Hp et les groupes sanguins (ABO, MN, Rh), les protéines sériques (groupe Gm) et la sensibilité gustative à la phénylthiocarbamide (PTC).

Acknowledgements: We wish to express our gratitude to Professor *N. Oker-Blom*, Head, Department of Virology, University of Helsinki who kindly placed a part of the blood samples at our disposal; to Dr. *F. Galatius-Jensen*, University Institute of Forensic Medicine, Copenhagen, and Fil. Mag. *Evi Fleisher*, University Institute of Forensic Medicine, Oslo, for their advice and help during the work; to Miss *Eeva Salonen* for skilful technical assistance; and to Miss *M.-L. Blom* for help during the collection of the material.

REFERENCES

1. *Allison, A.C.; Blomberg, B.S. and Mrs. ap Rees.:* Haptoglobin types in British, Spanish, Basque and Nigerian African populations. Nature *189:* 824 (1958).
2. *Beckman, L.:* Personal communication.
3. *Fleischer, E. and Lundevall, J.:* Inheritance of serum groups. Proc. 6th Congr. Europ. Soc. Haematol. Part 2, 907 (S. Karger, Basel/New York 1958).
4. *Galatius-Jensen, F.:* Further investigations of the genetic mechanism of the haptoglobins. Acta genet. *7:* 549 (1957).
5. *Galatius-Jensen, F.:* On the genetics of the haptoglobins. Acta genet. *8:* 232 (1958).
6. *Galatius-Jensen, F.:* Rare phenotypes in the Hp system. Acta genet. *8:* 248 (1958).
7. *Giblett, E.L.:* Haptoglobin types in American Negroes. Nature *183:* 192 (1959).
8. *Harris, H. and Kalmus, H.:* The measurement of taste sensitivity to phenylthiourea (P.T.C.). Ann. Eug. *15:* 24 (1949).
9. *Harris, H.; Robson, E.B. and Siniscalco, M.:* Atypical segregation of haptoglobin types in man. Nature *182:* 1324 (1958).
10. *Jayle, M.F.; Boussier, G. et Bain, J.:* Electrophorèse de l'haptoglobine et de son complexe hémoglobinique. Bull. Soc. Chim. Biol. *34:* 1063 (1952).
11. *Mäkelä, O. and Tiilikainen, A.:* Inheritance of the Gm serum group. Ann. Med. exp. Fenn. *37:* 180 (1959).
12. *Smithies, O.:* Grouped variations in the occurence of new protein components in normal human serum. Nature *175:* 307 (1955).

13. *Smithies, O.:* Zone electrophoresis in starch gels: group variations in the serum proteins of normal human adults. Biochem. J. *61:* 629 (1955).
14. *Smithies, O. and Walker, N.F.:* Genetic controll of some serum proteins in normal humans. Nature *176:* 1265 (1955).
15. *Smithies, O. and Walker, N.F.:* Notation for serum protein groups and the genes controlling their inheritance. Nature *178:* 694 (1956).
16. *Sutton, H.E.; Neel, J.V.; Binson, G. and Zuelzer, W.W.:* Serum protein differences between Africans and Caucasians. Nature *178:* 1287 (1956).

Authors' adress: Dr. O. Mäkelä, A. W. Eriksson and R. Lehtovaara, Department of Serology and Bacteriology, University of *Helsinki* (Finland).

APPENDIX

List of all families with both parents and at least one child tested

Key to appendix

Column I. Number of person

II. Sex (M = male, F = female). Brackets indicate twins.

III. Year of birth (last two figures only).

IV. Blood groups (anti-C, -D, -E, -c used for Rh grouping).

Key to Rh phenotypes:		Most likely genotype:
R1r R1Ro	= C+D+E—c+	CDe/cde CDe/cDe
R1R1 R1R′	= C+D+E—c—	CDeCDe CDe/Cde
rr	= C—D—E—c+	cde/cde
R1R2 R1R″	= C+D+E+c+	CDe/cDE CDe/cdE
R2r R2R2 R2Ro	= C—D+E+c+	cDE/cde cDE/cDE cDE/cDe
Ror	= C—D+E—c+	cDe/cde
R′r	= C+D—E—c+	Dde/cde
R″r	= C—D—E+c+	cdE/cde
R1Rz	= C+D+E+c—	CDe/CDE

V. Hp = Haptoglobin group, Hp 1–1, Hp 2–1, Hp 2–2, und. = undeveloped.

VI. Gm(a) = Gm serum group, Gm(a+), Gm (a—).

VII. PTC = Ability to taste phenylthiocarbamide. Numbers denote sequence of tubes: 1 and 2 indicate non-tasters, 3, 4, 5 and 6 tasters.

Within the families the parents are set out first.

I	II	III	IV	V	VI	VII
1	M	17	O M R1R2	2–2	a—	2
2	F	17	A1B M R2r	2–2	a—	4
3	M	42	B M R1R2	2–2	a—	2
4	M	44	A1 M R1R2	2–2	a—	2
5	F	46	A1 M R2r	2–2	a—	1
6	M	54	B M R2r	2–2	a—	
7	M	16	O N R1r	1–1	a+	4
8	F	19	B M R1r	2–1	a+	1
9	F	42	B MN R1R1	2–1	a+	5
10	F	47	O MN R1R1	1–1	a+	4
11	F	51	B MN rr	2–1	a+	4
12	F	56	B MN R1r	1–1	a+	3
13	M	89	O MN R1r	1–1	a+	
14	F	90	O N R1R2	2–1	a+	
15	F	22	O N R1R2	2–1	a+	
16	F	27	O N R1R1	1–1	a+	
17	M	21	O N R1R1	2–2	a—	5
18	F	19	O M R1r	2–2	a+	2
19	M	56	O MN R1R1	2–2	a+	
20	M	10	A1 M R1R1	2–1	a+	1
21	F	21	O MN rr	1–1	a+	4
22	M	41	O MN R1r	1–1	a+	4
23	F	44	O MN R1r	2–1	a+	3
24	M	48	O M R1r	2–1	a+	4
25	F	51	A1 MN R1r	2–1	a+	3
26	M	17	A1 M R1R2	2–1	a+	2
27	F	18	O N R1r	2–2	a+	4
28	F	40	O MN R2r	2–1	a+	4
29	M	42	O MN R2r	2–1	a+	3
30	F	46	O MN R1R1	2–1	a+	3
31	M	19	B M R1Ro	2–1	a—	4
32	F	22	O M R2r	2–1	a+	5
33	F	42	B M Ror	2–1	a+	5
34	M	47	B M R2Ro	2–1	a+	5
35	F	51	B M R1R2	2–1	a+	4
36	M	54	B M R1R2	2–2	a+	
37	M	11	O MN R2r	2–1	a+	3
38	F	13	O N R1r	2–1	a—	4
39	M	40	O MN R2r	1–1	a+	
40	F	44	O N R1r	2–1	a—	4
41	M	54	O MN R1r	2–2	a+	
42	M	86	A1 M R1r	2–2	a—	2
43	F	96	A1 M R1R1	2–1	a+	1
44	M	27	A1 M R1r	2–1	a—	

I	II	III	IV	V	VI	VII
44	M	27	A1 M R1r	2–1	a—	
45	F	32	B M R1R2	2–1	a—	
46	F	53	A1B M R1r	2–1	a—	
47	M	54	O M R1R2	2–1	a—	
48	M	56	A1B M R1R1	2–2	a—	
49	F	58	A1B M R1R1	1–1		
50	M	07	O MN R1R1	2–2	a—	5
51	F	13	A2 MN R1r	2–1	a—	2
52	M	35	A2 N R1R1	2–2	a—	2
53	M	36	O N R1R1	2–1	a—	1
54	M	38	O M R1r	2–2	a—	2
55	F	45	O MN R1r	2–2	a—	5
56	M	22	A1 N R2r	2–2	a+	1
57	F	25	O M R1R1	2–1	a+	4
58	M	46	A2 MN R1r	2–2	a+	3
59	M	53	O MN R1r	2–2	a+	
60	F	55	A2 MN R1R2	2–1	a+	
61	M	94	O M R2r	2–1	a—	4
62	F	00	O MN R1r	2–2	a+	1
63	M	23	O M R1r	2–2	a+	1
63	M	23	O M R1r	2–2	a+	1
64	F	23	O N R1R1	2–1	a—	4
65	M	55	O MN R1r	2–1	a+	
66	M	57	O MN R1R1	2–2	a—	
67	M	18	A2 MN R1R2	1–1	a+	1
68	F	19	O MN rr	2–1	a—	5
69	F	43	O N R2r	1–1	a+	2
70	M	45	A2 N R2r	2–1	a+	1
71	M	53	A2 M R1r	1–1	a+	
72	F	56	A2 N R1r	1–1	a+	2
73	M	90	O M R1r	2–1	a+	4
74	F	96	O M R1R1	2–2	a—	3
75	M	19	O M R1r	2–1	a+	5
75	M	19	O M R1r	2–1	a+	5
77	F	19	O N R1R1	2–1	a+	5
78	F	48	O MN R1r	2–2	a—	4
79	F	52	O MN R1R1	2–1	a+	3
80	M	54	O MN R1R1	2–1	a+	
81	M	09	O MN R1r	1–1	a+	3
82	F	21	A1 M rr	2–1	a—	4
83	M	44	A1 MN R1r	1–1	a+	
84	M	53	A2 M rr	1–1	a+	3

I	II	III	IV	V	VI	VII
85	M	22	A1 MN R1R2	2–1	a+	2
86	F	22	O N R1r	2–2	a+	5
87	M	52	O N R2r	2–1	a+	5
88	M	55	O MN R1r	2–2	a+	
89	M	56	A1 N R2r	2–1	a+	
90	M	58	A1 MN R1R2	2–1		
91	M	19	A1 MN R1R2	2–1	a+	4
92	F	19	O M R1r	2–2	a+	5
93	F	47	O MN R1R1	2–2	a+	4
94	M	48	A1 MN R1R2	2–2	a+	4
95	M	49	O MN R2r	2–1	a—	4
96	M	58	O MN R1R2	2–2		
97	M	12	A1 M R1R1	2–1	a+	5
15	F	22	O N R1R2	2–1	a+	5
98	F	41	O MN R1R2	1–1	a+	4
99	M	46	A1 MN R1R2	2–1	a+	4
100	M	02	O M Ror	1–1	a+	3
101	F	08	O N R1r	2–2	a+	3
102	M	37	O MN R1r	2–1	a—	4
103	F	35	O MN Ror	2–1	a+	1
104	M	05	O M R1r	2–1	a—	4
105	F	08	A1 N R1r	2–2	a—	5
106	M	42	A1 MN rr	2–2	a—	1
107	M	92	A1 M R2r	2–2	a—	2
108	F	96	O MN R1r	2–2	a+	5
109	M	23	A1 M R2r	2–2	a—	4
110	F	31	A1 MN rr	2–2	a—	3
111	M	22	A1 M rr	2–1	a+	4
16	F	27	O N R1R1	1–1	a+	1
112	M	49	O MN R1r	2–1	a—	3
113	M	56	O MN R1r	1–1	a+	
114	M	11	O MN R1r	2–1	a—	3
115	F	09	A1 M rr	1–1	a—	3
116	M	46	A1 MN rr	2–1	a+	5
117	M	49	A1 MN R1r	2–1	a+	4
118	M	21	A1 N rr	2–2	a+	2
119	F	20	A2B M R1r	2–2	a—	1
120	M	44	A	2–2	a—	
121	F	45	A	2–2	a—	
122	M	91	A	2–1	a+	1
123	F	97	B	2–1	a+	4
124	F	28	B	1–1	a+	5
125	M	30	B	2–1	a—	5
126	F	38	B	1–1	a+	1

I	II	III	IV	V	VI	VII
127	M	83	O MN R1R2	2–1	a—	2
128	F	80	O M R1R1	2–2	a+	5
129	M	10	O M R1R1	2–2	a+	3
130	M	99	A2 N rr	2–2	a+	2
131	F	04	A1 MN R1r	2–1	a+	5
132	F	32	A1 N R1r	2–1	a+	3
133	F	42	A1 MN rr	2–2	a+	5
134	M	98	A2B N rr	2–1	a—	4
135	F	03	A1 MN R1r	2–1	a+	5
136	M	44	A2 N rr	2–1	a+	5
137	F	36	A1B N R1r	1–1	a—	5
138	M	09	A1 N R1r	2–1	a+	5
139	F	13	A2 M R1r	2–2	a+	6
140	F	42	A1 MN rr	2–2	a+	6
141	M	85	O MN R1R1	2–2	a—	4
142	F	85	B N R1R1	2–1	a—	4
143	F	14	B MN R1R1	2–2	a—	5
144	M	22	O N R1R1	2–1	a—	4
145	M	99	A2 MN R1R2	2–2	a+	1
146	F	02	O M R1R1	2–1	a—	5
147	M	23	O M R1R2	2–1		
148	F	24	A2 M R1R2	2–1	a—	5
149	M	28	A2 MN R1R1	2–1	a—	4
150	F	33	O MN R1R1	2–2	a—	5
151	M	34	A2 M R1R1	2–1	a+	4
152	M	09	A2 MN R1r	2–2	a—	1
143	F	14	B MN R1R1	2–2	a—	5
154	M	35	B M R1r	2–2	a—	4
155	M	41	A2B MN R1R1	2–2	a—	5
156	M	47	O MN R1r	2–2	a—	4
157	M	07	A1 N R1R2	2–2	a+	1
158	F	11	A1 N R1R2	2–2	a+	4
159	M	31	A1 N R1R1	2–2	a+	4
160	M	36	A1 N R1R2	2–2	a+	4
161	M	17	A2 MN R2r	2–1	a+	
162	F	20	A2 N R1R2	2–2	a—	
163	F	44	O N R1r	2–1	a+	
164	F	47	A2 MN R1r	2–2	a+	
165	M	53	O MN R1R2	2–1	a+	
166	M	76	A1 N R1r	2–1	a+	3
167	F	86	O MN R1R1	2–1	a—	1
168	M	12	A1 MN R1R1	2–1	a—	1
169	F	15	A1 N R1r	2–1	a+	1
170	M	16	O N R1r	2–1	a—	3

I	II	III	IV	V	VI	VII
168	M	12	A1 MN R1R1	2–1	a—	1
171	F	11	O M R1r	1–1	a+	1
172	F	39	O M R1R1	2–1	a+	1
170	M	16	O N R1r	2–1	a—	3
173	F	17	B MN R1r	2–2	a+	1
174	M	47	B N rr	2–2	a+	1
175	M	22	O M R1R2	2–2		4
176	F	25	O MN R1r	2–1		5
177	F	46	O M R1r	2–1		4
178	M	48	O M R1R1	2–2		2
179	M	49	O MN R1R1	2–1		4
180	M	54	O M R1R2	2–1		4
181	M	19	O M R1R1	2–2		3
182	F	22	A1 N R1R2	2–1		3
183	F	46	O MN R1R2	2–2		3
184	F	48	O MN R1R2	2–2		2
185	M	19	A1 MN rr	2–2		5
186	F	16	A2 MN R1r	2–2		5
187	M	43	A2 N rr	2–2		5
188	F	46	O MN R1r	2–2		4
189	M	00	A1 MN R1r	2–1		5
190	F	04	O MN R1r	2–2		5
191	M	34	O M rr	2–1		4
192	F	36	O N R1r	2–2		4
193	F	44	A1 MN R1r	2–2		5
194	M	81	B M R1R1	2–2		3
195	F	94	O M rr	2–1		4
664	F	19	O M R1r	2–2		5
196	M	26	B M R1r	2–1		4
197	M	30		2–2		
198	M	38	B M R1r	2–1		5
199	M	23	O MN R1r	2–2		3
200	F	30	O MN R1R1	2–1		4
201	F	50	O MN R1R1	2–1		4
202	F	53	O N R1R1	2–1		4
203	M	06	A1 MN R1r	2–1		1
204	F	10	A M R1r	2–1		1
205	M	34	O MN rr	1–1		2
206	M	10	A1 M R1r	2–1		4
207	F	11	O MN R1R1	2–1		4
208	F	43	O MN R1r	2–1		4
209	M	47	A1 MN R1r	2–1		4
210	M	20	O M R1R1	2–1		1
211	F	30	A1 M R1r	2–1		5
212	M	51	A1 M R1R1	2–1		2
213	F	54	A1 M R1R1	2–1		1
214	M	95	O M R1R2	2–1		3
215	F	95	A1 MN R1R2	2–2		4
216	M	23	A1 MN R2R2	2–2		4
217	M	26	A1 N R2r	2–1		4
218	F	26	A2 MN R2r	2–2		2
219	F	55	A1 N R2r	2–2		
220	M	12	O M R2r	2–1		4
221	F	16	B MN rr	1–1		6
222	F	46	B MN rr	1–1		5
223	M	91	A1 MN R1R1	2–1		3
224	F	92	A1 M R1R1	2–1		1
225	M	18	A1 M R1R1	2–1		1
226	F	19	A1 M R1R1	1–1		2
227	F	20	A1 MN R1R1	1–1		2
228	M	27	O MN R1R1	2–2		3
229	M	07	O MN R1r	2–2		4
230	F	08	A1 MN rr	2–2		3
231	M	33	A2 MN R1r	2–2		4
232	M	38	O MN rr	2–2		5
233	F	39	O N R1r	2–2		3
234	M	41	O N R1r	2–2		4
235	M	43	A1 N rr	2–2		4
236	M	46	O MN rr	2–2		5
237	F	48	A1 MN R1r	2–2		4
238	M	86	A1 MN R1R1	2–2	a+	
239	F	04	O M R2r	2–2	a+	
240	M	33	A1 MN R1r	2–2	a+	
241	M	34	A1 M R1R2	2–2	a+	
242	M	36	A1 MN R1r	2–2	a—	
243	M	38	A1 M R1R2	2–2	a+	
244	M	41	A1 MN R1r	2–2	a+	
245	M	43	A1 M R1R2	2–2	a+	
246	M	07	B MN R1r	2–2	a—	
247	F	09	A1 M R1R1	2–2	a+	
248	F	35	A1 MN R1r	2–2	a+	
249	M	37	A1B M R1R1	2–2	a—	
250	F	41	O MN R1r	2–2	a+	
251	M	44	O M R1r	2–2	a+	
252	F	47	B MN R1R1	2–2	a+	

I	II	III	IV	V	VI
253	M	03	O N R1 R2	2–2	a+
254	F	04	A1B M R1r	2–1	a+
255	F	34	A1 MN R1R2	2–1	a—
256	M	36	A1 MN R1R2	2–2	a+
257	F	38	B MN R2r	2–2	a—
258	F	43	A1 MN R1R2	2–1	a+
259	F	32	B MN R1R2	2–2	a+
260	M		B M R1r	2–2	a+
261	F		O MN R1r	2–2	a+
262	F		B MN R1r	2–2	a+
263	M		O MN R1R1	2–2	a+
264	M		O M R1r	2–2	a+
265	M		B MN R1R2	2–2	a+
266	F		O MN R1r	2–2	a—
267	M		B N R1R2	2–2	a—
268	M		B MN R1R2	2–2	a+
269	M		O N R1R2	2–2	a—
270	M		O N R1R2	2–2	a+
271	M		O N R1r	2–2	a+
272	M		A1 M R1R1	1–1	a+
273	F		A1 MN R1R2	2–1	a—
274	M		A1 M R1R1	2–1	a+
275	F		O MN R1R2	1–1	a+
276	M		O MN R1R2	1–1	a+
277	M	03	B M R2r	2–2	a—
278	F	11	O M R′r	2–1	a+
279	F	39	B M R′R2	2–1	a+
280	F	39	B M R′R2	2–1	a+
281	M	45	O M rr	2–2	a+
282	M	03	A2 M R1R1	2–1	a+
283	F	08	O N R1r	2–2	a+
284	M	35	A2 MN R1R1	2–1	a+
285	F	39	O MN R1r	2–2	a+
286	F	45	O MN R1r	2–2	a+
287	M		A1 M rr	2–1	a+
288	F		O M R1r	2–1	a—
289	M		A1 M R1r	1–1	a—
290	F		A1 M rr	2–1	a—
291	M		A1 M R1r	1–1	a—
292	F		A1 M R1r	2–1	a—
293	M	05	O M R1r	1–1	a—
294	F	08	O M R1r	2–2	a—
295	M	36	O M R1r	2–1	a—
296	M	40	O M R1r	2–1	a—
297	F	46	O M R1R1	2–1	a—
298	M		B M R2r	2–2	a+
299	F		O M R1r	2–1	a+
300	M		B M R1r	2–1	a+
301	F		B M R2r	2–2	a—
302	M		B M R1R2	2–1	a+
303	M		B M R1R2	2–1	a—
304	M	06	B MN R1r(Ro)	2–2	a+
305	F	10	O MN R1r(Ro)	2–1	a+
306	F	35	B N R1R1	2–1	a+
307	F	34	B MN R1r	2–2	a+
308	F	37	B M Ror	2–1	a+
309	F	43	O N Ror	2–2	a+
310	F	49	O MN Ror	2–1	a+
311	M	48	O MN R1r	2–2	a+
312	M	03	A2B MN R1r	2–1	a+
313	F	11	O M R'r	2–1	a+
314	M	34	A2 MN R′r	2–2	a+
315	F	40	A2 MN R′r	2–1	a+
316	F	42	A2 MN rr	2–1	a+
317	M	08	A2 MN rr	2–2	a—
318	F	15	O M R1R1	2–1	a—
319	M	41	A2 MN R1r	2–2	a—
320	F	43	A2 M R1r	2–2	a—
321	F	45	A2 MN R1r	2–1	a—
322	M	12	O MN rr	2–1	a+
323	F	13	A1 MN R1R1	2–2	a—
324	F	38	A1 MN R1r	2–1	a+
325	M	41	O M R1r	2–2	a—
326	M	47	A1 MN R1r	2–2	a+
327	M	09	O M R2r	2–1	a—
328	F	14	O MN R1r	2–2	a+
329	M	41	O MN R2r	2–2	a+
330	M	45	O MN rr	2–1	a+
331	F	46	O M rr	2–1	a+
332	M	07	B MN R2r	2–2	a+
333	F	11	A1B MN R1R1	2–1	a+
334	F	41	A1B M R1r	2–1	a+
335	M	44	A1B N R1R2	und.	a—
336	F	45	A1B N R1R2	2–1	a+
337	M	13	O MN R1r	2–1	a+
338	F	12	A1 MN R1R1	2–2–	a+
339	F	39	A1 N R1r	2–2	a+
340	M	44	O M R1R1	2–1	a+
341	M	50	A1 MN R1r	2–2	a+

I	II	III	IV	V	VI
342	M		O M rr	2–2	a+
343	F		A2 MN Ror	2–1	a+
344	F		O M rr	2–2	a+
345	F		O MN rr	2–1	a+
346	M		A2 MN rr	2–2	a+
347	M	20	A1 N rr	2–2	a+
348	F	26	A2B M rr	1–1	a+
349	M	47	B MN rr	2–1	a+
350	F	49	B MN rr	2–1	a+
351	M	51	A1B MN rr	2–1	a+
352	F	52	A2 MN rr	2–1	a+
353	M	53	B MN rr	2–1	a+
354	M	54	B MN rr	2–1	a+
355	F	56	A1B MN rr	2–1	a+
356	M	58	B MN rr	2–1	a+
357	M		A1 N R1r	1–1	a+
358	F		A1 M R1r	2–1	a+
359	M		A1 MN rr	1–1	a+
360	M		A1 MN R1r	2–1	a—
361	F		A1 MN R1R1	2–1	
362	F		A1 MN rr	1–1	a+
363	F		A1 MN R1R1	2–1	a+
364	M	18	B MN rr	2–2	a+
365	F	10	B MN Ror	2–2	a+
366	M	43	B MN Ror	2–2	a+
367	F	45	B MN Ror	2–2	a+
368	M	47	B M rr	2–2	a+
369	M	49	B MN Ror	2–2	a+
370	M	50	B Mrr	2–2	a+
371	M	15	A1 M R1r	2–2	
372	F	17	B N Ror	2–2	
273	F	39	B MN R1r	2–2	
374	F	45	O MN R1r	2–2	
375	F	46	O MN Ror	2–2	
376	M	48	B MN R1r	2–2	
377	M	50	O MN rr	2–2	
378	M	51	A1 MNRor	2–2	

I	II	III	IV	V
379	M	04	A2 N rr	2–2
380	F	07	O N R1R1	2–1
381	M	32	O N R1r	2–2
382	F	33	A2 N R1r	2–1
383	F	35	O N R1r	2–1
384	F	36	A2 N R1r	2–2
385	M	39	A2 N R1r	2–1
386	F	42	O N R1r	2–1
387	F	47	O N R1r	2–1
388	F	49	O N R1r	2–1
389	M	98	B MN rr	2–1
390	F	04	O MN rr	2–2
391	F	28	B MN rr	2–1
392	M	34	B MN rr	2–1
393	M	40	B M rr	2–1
394	F	41	B M rr	2–2
395	M	46	B N rr	2–1
396	M	49	B N rr	2–1
397	M	22	A2 M R1R1	1–1
398	F	27	O MN R1R1	2–2
399	M	47	A2 M R1R1	2–1
400	F	48	O MN R1R1	2–1
401	M	52	O MN R1R1	2–1
402	F	55	A2 MN R1R1	2–1
403	M	05	A1 MN R1R1	2–2
404	F	06	B MN R2r	2–2
405	F		A1B MN R1r	2–2
406	F	35	A1B MN R1r	2–2
407	M	42	A1 N R1r	2–2
408	M	44	O MN R1R2	2–2
409	M	46	A1B MN R1r	2–2
410	F	48	A1B MN R1r	und.
411	M	49	A1B M R1R2	2–2
412	M	51	B M R1R2	2–2
413	M	21	A MN R1r	2–1
414	F	25	A M rr	2–1
415	F	48	A M rr	2–1
416	F	49	A MN rr	2–2
417	F	50	A M rr	2–1
418	M	95	O MN R1R2	2–1
419	F	04	A M R1R2	2–1
420	M	35	A M R1R2	2–2
421	M	42	A MN R1R2	2–1
422	M	44	A M R1R2	2–1
423	F	46	O MN R1R2	2–2

I	II	III	IV	V
424	M	18	O MN R1r	2–2
425	F	22	O MN rr	2–2
426	M	49	O M R1r	2–2
427	F	53	O N R1r	2–2
428	M	11	A MN R1R2	2–2
429	F	20	A MN R1r	1–1
430	M	44	A MN R1r	2–1
431	F	46	A M R1R2	2–1
432	M	50	A N R1R2	2–1
433	M	20	A1 MN rr	2–2
434	F	18	O N R1r	1–1
435	F	46	A1 N rr	2–1
436	M	47	A1 MN R1r	2–1
437	F	51	A1 MN R1r	2–1
438	F	53	A1 N rr	2–1
439	M	06	A1 MN rr	2–2
440	F	18	B MN R1R1	2–2
441	M	41	O MN R1r	2–2
442	F	47	A1 MN R1r	2–2
443	M	48	B MN R1r	2–2
444	F	49	B MN R1r	und.
445	F	50	A1 MN rr	2–2
446	F	52	O MN R1r	2–2
447	M	53	B MN R1r	2–2
448	M	55	O N R1r	2–2
449	M	03	A1 MN R1R1	2–1
450	F	16	O MN R1r	2–2
451	F	43		2–2
452	F	44	A1 M R1R1	2–1
453	M	46	A1 N R1r	2–1
454	F	48	O M R1R1	2–2
455	M	49	A1 MN R1R1	2–1
456	M	51	O MN R1r	2–1
457	F	53	A1 MN R1r	2–2
458	M	12	A1 M R1R2	1–1
459	F	20	A1 N R1R1	2–1
460	F	47	A1 MN R1R1	2–1
461	F	48	A1 MN R1r	2–1
462	F	50	A1 MN R1r	2–1

I	II	III	IV	V
463	M	00	O M R2r	2–2
464	F	12	A1B MN R1r	2–2
465	M	33	B MN R1R2	2–2
466	F	43	B MN R1R2	2–2
467	M	45	A1 M R1R2	2–2
468	M	47	A1 M R2r	2–2
469	F	51	B MN R1r	2–2
470	F	52	B MN R1R2	und.
471	M	12	A1 N R2r	1–1
472	F	15	O M R1r	2–2
473	F	37	A1 MN R1r	2–1
474	F	40	O MN R1r	2–1
475	M	42	A1 MN R1R2	2–1
476	F	44	O MN R2r	2–1
477	M	46	O MN R1R2	2–1
478	M	50	A1 MN R1R2	2–1
479	M	20	A1 M R1R1	2–2
480	F	20	A1 MN rr	2–2
481	M	44	A1 MN R1r	2–2
482	F	46	A1 M R1r	2–2
483	F	48	A2 MN R1r	2–2
484	F	49	A1 MN R1r	2–2
485	M	12	O M R2r	1–1
486	F	26	A1 M R1R2	2–1
487	F	45	O M R1R2	1–1
488	M	45	A1 M R1r	1–1
489	F	47	O M R1R2	1–1
490	F	49	A1 M R1r	1–1
491	M	50	A1 M R2r	2–1
492	M	90	O MN rr	1–1
493	F	93	A2B M R1R2	2–1
494	M	19	A2 MN R1r	1–1
495	F	22	A2 M R2r	1–1
496	F	24	B M R1r	2–1
497	F	26	A2 MN R1r	1–1
494	M	19	A2 MN R1r	1–1
498	F	18	B MN rr	2–1
499	M	45	A2 N rr	1–1
500	M	50	A2 M R1r	1–1
501	F	55	B M R1r	2–1
502	M	77	A1B M rr	2–1
503	F	97	O MN R1r	2–1
504	M	16	A1 M R1r	1–1
505	M	20	B MN rr	2–1
506	M	28	A1 M rr	1–1
507	M	30	B MN R1r	2–1

I	II	III	IV	V
505	M	20	B MN rr	2–1
495	F	22	A2 M R2r	1–1
508	M	48	B MN rr	1–1
509	F	49	A2B M rr	1–1
504	M	16	A1 M R1r	1–1
510	F	17	O M R1r	2–1
511	M	40	O M R1r	1–1
512	F	42	A1 M rr	2–1
513	F	46	O M R1r	2–1
514	F	48	A1 M R1r	1–1
515	M	53	O M R1r	2–1
516	M	96	A1 N R2r	1–1
517	F	92	O N R1R1	1–1
518	F	23	A1 N R1r	1–1
519	M	09	A2 MN R1R1	2–2
518	F	23	A1 N R1r	1–1
520	F	44	A2 N R1r	2–1
521	F	46	A1 MN R1r	2–1
522	M	48	O MN R1R1	2–1
523	M	08	A1 N R1r	2–1
524	F	12	A2 N R1R1	2–1
525	M	38	A1 N R1r	2–2
526	F	39	A2 N R1R1	2–2
527	M	46	A1 N R1R1	2–1
528	M	49	A2 N R1r	1–1
529	M	85	O MN R1r	2–1
530	F	88	A1 M R1r	2–2
531	F	09	A1 MN R1r	2–1
532	M	95	A1 N rr	1–1
533	F	02	A1 MN rr	2–1
534	F	23	O MN rr	1–1
535	F	24	A1 MN rr	1–1
536	M	27	A1 N rr	1–1
537	M	19	A1 N R2R′	2–2
535	F	24	A1 MN rr	1–1
538	F	46	O N R′r	2–1
539	M	15	O MN R1r	2–1
540	F	22	A1 MN R1r	2–1
541	M	43	A1 MN rr	2–1
542	M	92	O MN R1r	2–2
543	F	04	B MN R1r	2–2
544	M	32	O N R1r	2–2
545	M	34	B N R1R1	2–2
546	M	36	B M rr	2–2
547	F	41	B M R1r	2–2
548	M	92	B MN R1r	2–1
549	F	93	A1B M R2r	1–1
550	F	17	A1B MN rr	1–1
551	M	19	A1B M R2r	2–1
552	F	29	B MN R1R2	2–1
551	M	19	A1B M R2r	2–1
553	F	24	O M rr	2–1
554	M	43	A1 M R2r	1–1
555	F	44	B M R2r	2–1
556	F	46	B M R2r	2–1
557	M	83	O N R1r	1–1
558	F	86	A1 M R1R2	2–2
559	F	07	A1 MN R1R1	2–1
560	M	08	O MN R1r	2–1
561	M	09	A1 MN R2r	2–1
562	M	12	O MN R2r	2–1
563	F	20	A1 MN R1r	2–1
564	M	35	A1 MN R1R1	2–1
560	M	08	O MN R1r	2–1
565	F	27	O N R1r	2–2
566	F	52	O N R1R1	2–1
561	M	09	A1 MN R2r	2–1
567	F	22	A1 N rr	1–1
568	M	42	O N R2r	2–1
569	F	52	A1 N R2r	2–1
570	M	18	O MN R1r	2–1
571	F	18	O N R1R2	2–2
572	M	45	O N R1R1	2–2
573	M	48	O MN R1R2	2–2
574	M	51	O N R1R1	2–2
575	M		O MN R1R1	2–1
576	M	11	A1B MN R1r	2–2
577	F	16	O MN rr	2–2
578	F	42	A1 MN R1r	2–2
579	M	43	B M rr	2–2
580	M	45	A1 N rr	2–2
581	M	47	B M R1r	2–2
582	F	51	A1 N R1r	2–2

I	II	III	IV	V
583	M	09	B M R1R1	2–2
584	F	18	B MN rr	2–1
585	F	39	B M R1r	2–2
586	F	40	B MN R1r	2–2
587	F	41	B MN R1r	2–1
588	M	44	B M R1r	2–1
589	F	45	B MN R1r	2–2
590	F	48	B M R1r	2–2
591	M	50	B MN R1r	2–1
592	M	84	A1 MN R1R2	2–2
593	F	89	A1B MN R1r	2–1
594	M	14	B M R1r	2–2
595	F	21	B M R1R2	2–2
596	M	27	A1 MN R1r	2–2
597	M	34	A1 N R1R1	2–2
598	M	75	O N R1r	1–1
599	F	85	O MN R2r	2–1
600	M	14	O N R1r	1–1
601	M	16	O N R1R2	1–1
602	M	19	O N rr	2–1
603	M	12	A2 N R1r	2–1
604	F	11	O N R2r	1–1
605	F	45	A2 N R1r	1–1
606	M	46	O N R1r	1–1
607	F	47	A2 N R1r	1–1
608	M	18	O MN R2r	2–2
609	F	19	A1 M R1r	2–1
610	F	45	A1 MN R2r	2–1
611	M	46	A1 M R1R2	2–1
612	M	50	O MN rr	2–2
613	M	79	A2B MN R1R2	2–1
614	F	84	A1 M R1r	2–1
615	M	10	A1 M R1r	1–1
616	F	11	A1B MN R1R1	2–1
617	M	15	A2 M R1r	1–1
617	M	15	A2 M R1r	1–1
618	F	21	O N R1R1	2–1
619	F	46	O MN R1R1	2–1
620	F	51	O MN R1R1	2–1
615	M	10	A1 M R1r	1–1
621	F	12	O MN R1r	2–1
622	F	42	A1 MN R1R1	1–1
623	F	44	A2 MN rr	2–1

I	II	III	IV	V
624	M	12	A1 N rr	2–1
616	F	11	A1B MN R1R1	2–1
625	M	43	A1 MN R1r	2–1
626	M	44	A1B N R1r	2–1
627	F	45	A1 MN R1r	1–1
628	M	97	A1 MN R1R2	2–1
629	F	98	A2 N R1R1	2–2
630	F	28	O MN R1R2	2–1
631	M	32	O MN R1R1	2–1
632	F	39	A1 MN R1R1	2–2
633	M	17	A1 MN R1R1	2–2
634	F	23	A1 M R1R1	2–2
635	F	42	O M R1R1	2–2
636	F	43	A1 MN R1R1	2–2
638	M	17	O M R2r	1–1
639	F	25	O MN R2r	2–2
640	F	58	O M R2r	2–1
641	M	22	A1 MN R1R2	2–2
642	F	20	O M R1R1	2–2
643	F	46	O MN R1R2	2–2
644	M	48	O M R1R2	2–2
645	F	55	O M R1R2	2–2
646	M		A2 MN	1–1
647	F		A1 M	2–2
648	F		A1 M	2–1
649	F		A1 MN	2–1
650	M		A1 N	2–1
651	F		A1 MN	2–2
652	F		A1 N	2–2
653	M		A1 MN	2–2
654	M	22	A1 MN rr	2–1
655	F	15	O M R2r	2–2
656	M	49	O MN R2r	2–1
657	F	53	A1 MN rr	2–2
658	M	55	A1 MN R2r	2–1
659	F	57	O MN R2r	2–1
660	M	28	A2 M R2r	2–1
661	F	24	B N R2r	2–2
662	F	57	A2B MN rr	2–1
663	F	58	A2B MN rr	2–2

LIBRI

Ronald A. Fisher: **The Genetical Theory of Natural Selection.** 2nd Edition. Dover Publications, Inc., New York 1958. 292 pages. US$ 1.85.

The first edition of this small book was published in 1929, the second edition has appeared now nearly thirty years later, thoroughly revised by the author. In the first chapters the theorem of natural selection is dealt with. This part of the book is not easily read, but a thorough study is worth while because it gives the reader a clear insight into the mathematical background of the fundamental evolutional processes, mutation and selection. The latter part of the book is totally devoted to the problem of selection in man as a social animal with individualistic reproduction. The author takes the rather pessimistic view that civilizations are comdemned to deterioration because of the unhappy tendency of genes for low fertility to accumulate in the upper social layers in societies where private property is protected by civic law and a low number of children means a social advantage. On the contrary, in more primitive societies property will primarily be protected by the family and therefore, on an average the more numerous the families will be the more wealthy, and genes for high fertility will accumulate in the higher social layers. From a genetic standpoint the selective pattern in this primitive society will be the more favourable, and this may be the reason why barbarians repeatedly have been able to overrun peoples having a civilization higher than their own. This part of the book is fascinating reading, especially because of the strict logic sense of the author, but no matter how intriguing his theory may be, it seems to be based on rather inadequate empirical data.

B. Harvald, Copenhagen

F. Vogel: **Über die Erblichkeit des normalen Elektroencephalogramms.** Georg Thieme, Stuttgart 1958. 92 S., 25 Abb.

The question of the influence of hereditary factors in the development of the human brain wave pattern is of central importance in neurophysiology. The discussion of this subject, however, is delicate as it demands a thorough knowledge of genetics as well as a specialized training in electroencephalography. Dr. *Vogel* seems to comply with both demands. After a critical review of the literature on the subject he in this monograph presents his own series of altogether 208 pairs of adolescent twins. His scientific method has been perfect, both with regard to the zygosity diagnosis, where all known blood groups except Kell, Lutheran and the serum groups are used, and with regard to the evaluation of the EEG-findings. His description comprises not only the classification methods generally used, but for his special purpose he has developed an ingenious way of expressing the quantity of slow activity in his records. His results are quite clear: the normal brain wave pattern is in its whole construction completely determined by hereditary factors, a result which is in full agreement with the findings of *Lennox* and *Gibbs*. Unfortunately, the composition of his twin series (school children) did not allow the author to use Metrazol activation of the EEG; consequently, no conclusions could be drawn concerning the convulsive threshold, a problem of central importance for the study of heredity in epilepsy.

Considering the limited number of students in electroencephalography and the even more limited number of human geneticists, a simple calculation gives the very small number of students interested in genetics in electroencephalography. Nine tenths of this small number will, however, unfortunately be unable to read Dr. *Vogel*'s book as it is written in German, with legends of the tables in German and without even a short summary in English or French.

B. Harvald, Copenhagen

The Effects of Atomic Radiation on Oceanography and Fisheries. Nat. Acad. Sc. no. 551 - Nat. Research Council, Washington 1957. VII+137 p. $ 2.00.

This book is issued as a report from the Committee of the National Academy of Science on the Effects of Atomic Radiation on Oceanography and Fisheries, the chairman of which is R. Revellé. The chapters of the book are written by various members of the Committee, the contents being summarized in the first 25 pages.

The background radiation from the sea is 5—20‰ of that of the surface of the earth which on the basis of the immense volume of the sea should make the sea a safe place for dumping the radio-active waste from the Atomic Age. An important point is, however, the potent concentrating effect which may occur in the animal and plant kingdoms of the sea. Concentrating factors of up to one million have been found. It appears, however, permissible to dump 1,000 tons radio-active waste per year in the depths of the large oceans. In this connection it is mentioned that the water in the oceans circulates only so little that water from the great depths has an average stagnation time in the order of some hundred years. The calculations are, however, stated to be uncertain.

The ordinary chapters give an interesting picture of the methods employed by oceanographers and marine biologists but appear somewhat heterogeneous and with numerous repetitions. It is concluded that continued research in these fields is very necessary although expensive. *B. Zachau-Christiansen, Copenhagen*

Sonderausschuss Radioaktivität Bundesrepublik Deutschland. Erster Bericht (Jan. 1958). Georg Thieme, Verlag, Stuttgat 1958. 68 Seiten, 5 Abbildungen, 10 Tabellen. DM 4.50.

At the request of the authorities of the Federal Republic of Western Germany a committee of 12 members, mainly physicists, was set up in Germany on October 1st, 1956, which was charged with the task of elucidating the problems concerning the risks of ionizing radiation.

This committee has started a large scale research program, mainly on the radioactivity to be found in our surroundings and in the food. A full report of this work will be given later, but it has been considered desirable to publish the present book now, which is a preliminary report. In a number of extensive tables the results are given of measurements carried out in various German institutes during the year 1.10.1956–1.10.1957, showing the radioactivity found in the air, in dust, rainfall, water and milk. An increase has been noted here as in other parts of the world.

This report, which is only to be considered as an introduction to more extensive publications, is recommended to anyone who wants information about German research and points of view in this field. A full report comparable with the corresponding American and English reports from 1956 is promised; however, it seems as if it will be stamped by the physicists to a greater extent than the two other works mentioned.

B. Zachau-Christiansen, Copenhagen

Gerontologia Clinica

Internationale Zeitschrift für Geriatrie – International Journal of Geriatrics – Journal International de Gériatrie

1 volume of 4 numbers is published annually
Jährlich erscheint 1 Band von 4 Heften
1 volume à 4 fascicules paraît par année

Subscription price **per volume**
Abonnementspreis sFr. 38.50 **pro Band**
Prix d'abonnement **par volume**

BASEL (Schweiz) S. KARGER NEW YORK

L/Ag 5

EUGENICS QUARTERLY

Vol. 5, No. 4 December, 1958

CONTENTS:

Contributed Articles Welcome

Published by

AMERICAN EUGENICS SOCIETY

230 Park Avenue New York 17, N.Y.

Subscription: $5.00 — Membership: $5.00 — (Foreign: $2.50)